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AND

# NUCLEAR MEDICINE

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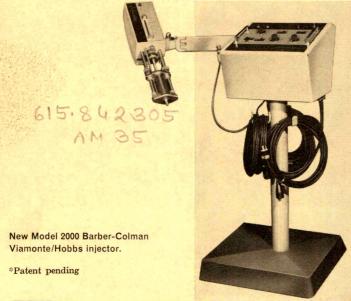
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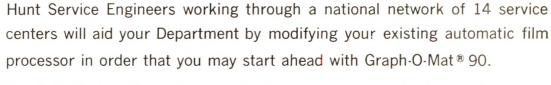




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\*Margulis, A. R., and Heinbecker, P.: Am. J. Roentgenol. 86:103 (July) 1961.

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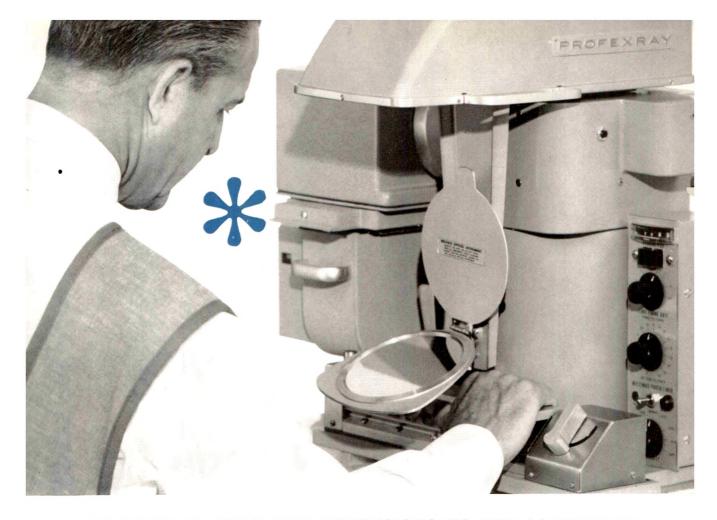
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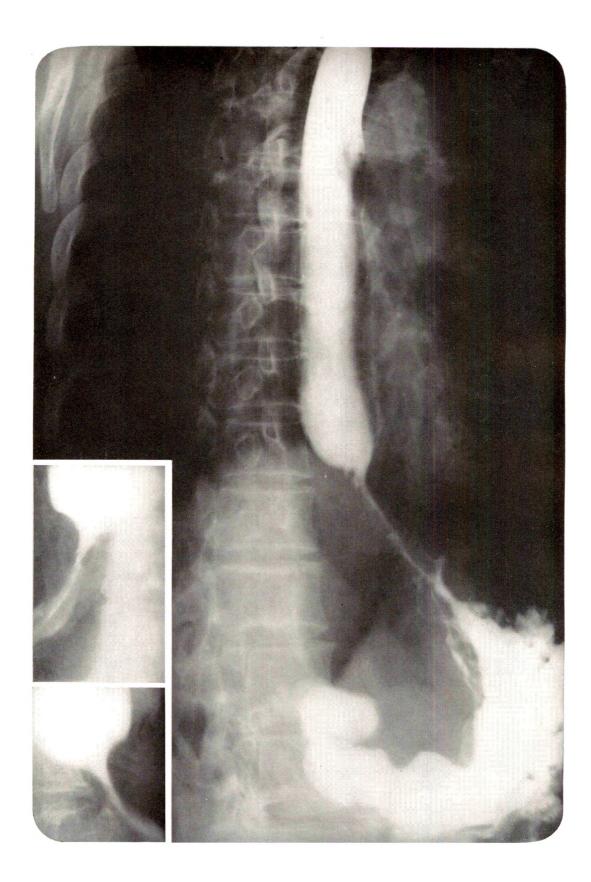
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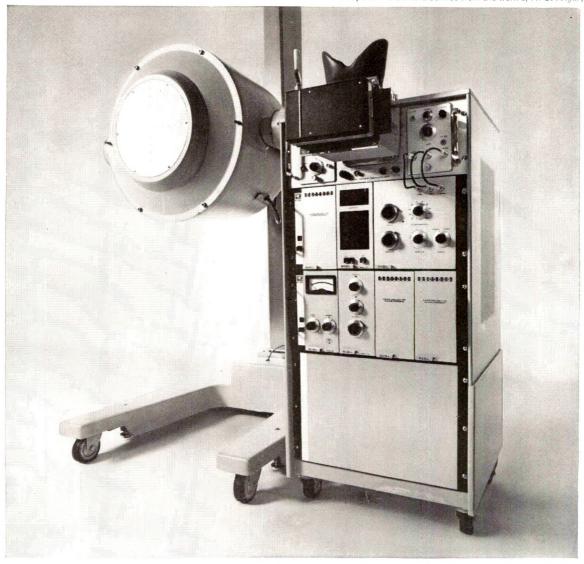
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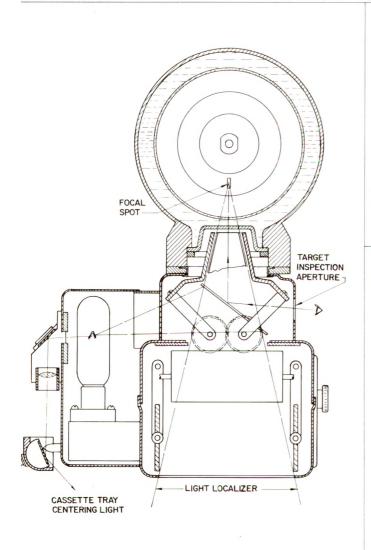
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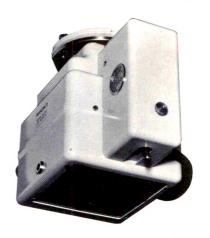






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T. A. WATSON Janeway Lecturer, 1965

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## CANCER OF THE BREAST\*

THE JANEWAY LECTURE—1965

By T. A. WATSON LONDON, ONTARIO, CANADA

It is a great honor and privilege to have been chosen to deliver the 1965 Janeway Lecture. On occasions such as these, it has been the custom to attempt to relate the topic in some way to the work or interest of the individual after whom the lectureship has been named. In the case of Henry Harrington Janeway such a relationship, applied to almost any aspect of cancer, is not hard to find because of his catholic interest in this field. In respect to the treatment of cancer of the breast, the subject of this address, he had quite definite ideas. In his report of 1917, in which the results of his pioneer radium treatment at the Memorial Hospital in 424 cases during the years of 1915 and 1916 were described, he included several patients with cancer of the breast. He was strongly of the opinion that the best treatment of early cancer of the breast consisted in a "proper" operation which he considered to be neither dangerous nor accompanied by serious deformity. Undoubtedly, from the context, a "proper" operation meant to him the Halstead mastectomy, and he thought incomplete operations to be hazardous. He advised against the use of radiation as the primary treatment excepting in inoperable or borderline inoperable cases.

Forty-eight years later these remain popular sentiments.

THE best management of early uncomplicated cancer of the breast has been the subject of fierce controversy in recent years. Formerly radical mastectomy, either alone or accompanied by pre- or postoperative radiation therapy had been the generally accepted treatment. It was not doubted that radical mastectomy was really a radical operation and that radiation therapy, applied to the chest wall and the areas of possible lymph node spread, was often efficacious in eradicating occult metastasis, direct spread beyond the operative field, or remnants of tumor remaining in the operated area.

It has now been variously suggested that local treatment of cancer of the breast does not affect the eventual inevitable fatal outcome in any case; that any effect of treatment is slight; that very local operations are equal to, or superior to radical operations; that radiation therapy is more important than surgery; and that supraradical surgery is the answer. Permutations and

<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

combinations of these principles, or the lack of them, have been advanced because of a general dissatisfaction with the results of the standard radical mastectomy with or without adjuvant radiotherapy. Patients so treated are known only too often to develop either local recurrence or distant metastases, sometimes after a long latent interval, with consequent steady, or occasionally intermittent, depending on response to the various palliative remedies, progression to death. Protagonists of one or other treatment modality tend to excess in vociferation, so that we are frequently amazed at the therapeutic passions aroused by what is, in spite of modern glamorization, an affliction of a superficial easily disposable utilitarian appendage.

My own views on this subject are reactionary and simple. The best management, using facilities, both human and mechanical, which are available and adequate almost everywhere, consists of radical mastectomy supplemented, when indicated by the clinical and pathologic findings, with postoperative radiotherapy. I do not propose to discuss the management of advanced or metastatic disease where the object of treatment is almost invariably palliative in nature.

Cancer of the breast is important because it is the commonest form of malignant disease in the female and because its management involves, at times, several medical disciplines. Although it can be classified as an "accessible" cancer, it frequently escapes early diagnosis and although extensive education programs have probably been successful in persuading more women to seek medical advice concerning lumps in the breast, the cynics point with misplaced unction at the lack of improvement in the survival rates when patients with recently discovered disease are promptly treated. It is true that the survival rate, as shown in many series, seems to be little affected by the duration of the disease prior to treatment, although figures from Saskatchewan (unpublished) and elsewhere3,28 show that survival is improved when the delay from

onset of first symptom to treatment is minimal. Such evidence, however, does not bear close scrutiny. Rapidly growing tumors occur probably more frequently among the "early diagnosed cases" because a sudden change is more likely to attract the attention of the hostesses, and thereby dictate more rapid action. Thus it would seem reasonable to assume that amongst cases treated with little delay from the first symptom there will be a higher proportion of rapidly growing and aggressive types of cancer. Until unequivocal evidence indicating that early treatment is not advantageous is produced, we must persist in the policy of immediate treatment as soon as the disease is diagnosed or suspected.

The contention that the course of cancer of the breast, as observed clinically, represents only a small part of the total history of the tumor is a rather disturbing concept. A number of investigators have taken serial measurements of tumors from roentgenograms, 7,10,24 and, after making the assumption that their growth had been exponential have predicted a time of origin of the tumor of many years prior to clinical discovery. Under these circumstances it would be a little absurd to insist on minimizing the delay from discovery of a tumor to treatment to a matter of days or a week or so, if the tumor had already been present a long time. If there had been prior opportunity for metastasis of several years' duration, the added risk of waiting a little longer would seem to be negligible. Our own studies16 of tumor growth in animals and fetal growth in humans suggest that growth deviates from an exponential law very early and more closely approximates a Gompertz function, as suggested by Laird.<sup>14</sup> We have concluded, therefore, that it is meaningless to fit a straight line to a semilogarithmic plot of growth data obtained over a short period of time, usually when the tumor is biologically large, and use it, by extrapolation, to predict the time of origin of the tumor or death of the host. Even "doubling times," obtained by such mathematical manipulations, are applicable only within

the time interval during which the data were collected (Fig. 1).

The strict applicability of the principle of indefinite exponential growth in human cancer of the breast, or malignant tumors in children, as originally proposed by Collins et al.7 would seem to be seriously compromised by data such as these, more especially in relation to breast cancer. It is conceivable that all tumors start growing exponentially. Soon, however, and perhaps at different sizes, according to histologic type and availability of nutritional supplies, the active growth is confined to the periphery of the tumor mass, and the growth curve changes its shape. If we have observed growth during only the latter part of the curve, therefore, and assume that the part of the graph which is available, is exponential, then extrapolation will grossly overestimate the total length of history of the tumor. It would therefore appear that early treatment will still be important in many patients.

When one is faced with a decision as to the choice of treatment in an early cancer of the breast, almost any course of action can be justified from the literature. It is extremely unlikely that each different management is of equal value, but it seems important that a standard treatment plan in the uncomplicated case should be formulated and followed. It must not be changed for any capricious whim or unreasoning prejudice. It may be argued that factors such as the site of the tumor in the breast. the coincidence of the menopause, early age or late age, or concomitant pregnancy, to mention but a few, should alter the planned treatment in early disease. Until, however, it has been conclusively demonstrated that cancer of the breast under one or other of these conditions is more favorably influenced by one modality of treatment than another, then the standard treatment plan should be slavishly followed. In fact, it is only by such consistency that any useful information will be obtained as to the influence of such factors on treatment. We simply do not have the information necessary

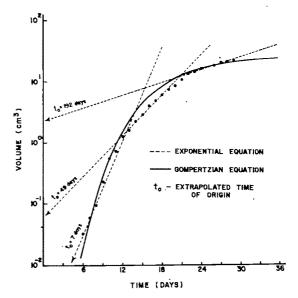


Fig. 1. Extrapolations of the growth curve of the C<sub>4</sub>HBA mouse mammary tumor.

to individualize treatment in operable disease, in spite of the current holiness of the concept.

Reasons for diversity of opinion regarding treatment of early disease are numerous, but difficult to specify accurately. One important cause of confusion arises from inability to compare the results of treatment by one method with those produced by another method. The clinical picture and biologic behavior of the tumor differ from patient to patient, and staging systems, theoretically useful in classifying the extent of the disease, vary from one center to another. Even if the same staging system is used (e.g., T.N.M.), interpretation of details varies so that, as is well known, comparison of results of treatment in similar stages between two institutions is likely to be inaccurate and misleading. The selection of cases for inclusion in a particular series is perhaps the greatest variable factor of all. This selection may be voluntary, when only certain patients are chosen for a certain type of treatment and the result of treatment in these cases only reported, or involuntary. Under the latter condition specific institutions may tend, because of their facilities, medical reputation, or administrative organization, to attract the referral of late cases in some instances and early cases in others.

A legitimate means of comparing two methods of treatment is to take all of the cases of cancer of the breast arising in a certain geographic region, and employ as a routine a certain method of treatment. No one method of treatment obviously can be applied to all cases but the method chosen should be applicable to the great majority of the patients suffering from the disease involved. Gross 5 year survival rates obtained in this way can then be compared with a similarly unselected group from another circumscribed area, in which a different main method of treatment is employed. This concept has been clearly enunciated and put into practice by McWhirter, 17 who has, for many years, been working in a center in Edinburgh to which almost all patients suffering from cancer of the breast in Southeastern Scotland are referred. A similar situation exists in Saskatchewan.

A comprehensive cancer program has been in operation in Saskatchewan since 1932, and through it, free treatment has been provided to all citizens of the province since 1944. Over 90 per cent of all cases of cancer occurring in the province are referred to one or other of two cancer clinics. It has previously been shown<sup>27</sup> that in the period 1944–1952 the coverage of all cases of cancer of the breast occurring in this region was as great, or greater, than that reported by McWhirter<sup>17</sup> from Southeast Scotland, using the same criteria of measurement.

During the years 1952–1959 an even greater percentage of all cases of cancer of the breast occurring in Saskatchewan was referred to these clinics. A continuous incidence study conducted by Barclay<sup>1,2</sup> over this period showed that the number of patients developing cancer of the breast, who were not referred to a cancer clinic and, therefore, do not appear in the statistics which are to be presented, amounted to 8 per cent of the total. Records of these patients were obtained from all pathologic laboratories in the province, from all hospitalization records in the province, and from all

death certificates. It is felt that in this way a complete tally of all cases of cancer of the female breast occurring in Saskatchewan during these years has been obtained. The number of new cases for each year is listed in Table 1, in an effort to indicate the total incidence of the disease in the province. It will be noted that the incidence apparently increases throughout the period under survey, there being a 22 per cent increase between 1952 and 1959. During this time the female population of the province increased moderately, to the extent of 8 per cent. The female population as a whole, however, has been aging, on balance, so that there has been an increase of over 12 per cent for those over 35 years of age, and the difference is more marked for older age groups, in which by far the greatest number of cases falls, so that there would seem to be good evidence that almost all cases occurring in the province are seen in the clinics, and that there can be no significant factor of case selection (Table II).

The management of early cancer of the breast in Saskatchewan during this period has been virtually uniform. Frozen section biopsy has been advised and carried out on

Table I

INCIDENCE\* OF CANCER OF THE FEMALE BREAST
IN SASKATCHEWAN
1952-1959

	Referred	to Clinics	Not		
Year	No previous treatment	Previous treatment adequate	Referred to a Clinic	Total	
1952	160	6	24	190	
1953	155	3	25	183	
1954	166	_	21	187	
1955	191		19	210	
1956	201	ĭ	14	216	
1957	211	2	16	229	
1958	210	3	7	220	
1959	216	2	13	231	
Total	1,510	17	139	1,666	

<sup>\*</sup> Excluding new cancers of the contralateral breast and non-residents of the province.

patients referred with localized solitary masses in the breast and radical mastectomy has almost invariably been undertaken when the frozen section pathologic report is positive, providing of course, that the disease is "operable." If the axillary lymph nodes are found to be involved, then postoperative radiation therapy to the axillary and supraclavicular lymph node areas in the affected side, as well as the internal mammary lymph node chain, has been routinely employed. In these cases the chest wall was not generally irradiated unless there was some special indication, such as wide invasion of the skin of the breast by tumor or deep infiltration of the underlying muscle. When the axillary lymph nodes were not involved, as shown by pathologic examination, postoperative radiation treatment was not given, excepting in cases in which the tumor was in the medial half of the breast or centrally situated. In these cases irradiation of the internal mammary lymph node chain only was accomplished with a single field, about 15×6 cm. in size, 280 kv., focal skin distance 50 cm., half value layer 2.5 mm. of copper, with a given dose of 4,000 r to 4,250 r in 15 treatments over a 3 week period. When secondary deposits were found at operation in the axilla, the axillary and supraclavicular lymph node areas were irradiated by parallel opposing fields, using either cobalt 60 irradiation at 80 cm. skin source distance, to a central

TABLE II

	Ali		Female Population of Saskatchewan		Inci-	
Year	Ages	Over 35 years of age	Over 50 years of age	Cancer of the Breast		
TOTO	402.700	7.48.000	76.400	700		
1952	403,7∞	148,900	76,400	190		
1953	413,1∞	152,5∞	78,∞∞	183		
1954	418,200	155,300	79,4∞	187		
1955	421,300	158,1∞	80,700	210		
1956	422,237	160,127	81,499	216		
1957	421,900	161,∞∞	82,200	229		
1958	427,5∞	163,300	83,900	220		
1959	436,∞∞	167,200	86,9∞	231		

Table III

CANCER OF THE FEMALE BREAST
SASKATCHEWAN 1952-1959

Description	Total	No. Sur- viving 5 Years	Per Cent 5 Year Sur- vival
All cases	1,510	880	58
Included (a) Not treated (b) Lost to follow-up	60 5	7	***************************************
Excluded			
(a) Previous treatment adequate	17	11	
(b) Cancer of male breast	11	7	
(c) New cancer of contralateral breast	57	29	51

dose of 4,000 r in 3 weeks, with equal daily doses; or 280 kv. at focal skin distance of 50 cm., with a central dose of 3,750 r, the over-all treatment time and fractionation being similar. The size of these fields in the horizontal direction varied from 15 to 20 cm. and vertically from 8 to 12 cm. Exceptions to this general plan of treatment were patients with grossly advanced local disease, in whom either preoperative irradiation or irradiation only was undertaken, cases in which surgical or medical contraindications existed and, of course, patients with metastatic disease beyond the axilla.

Because of my association with the Saskatchewan cancer program from 1946 until recently, the Saskatchewan Cancer Commission has kindly granted me permission to report on all cases of cancer of the breast seen in its clinics from 1952–1959, extending the period of prior reports on the years 1944–1952.<sup>26,17</sup> I am particularly indebted to Dr. T. C. F. Barclay of the Allan Blair Memorial Clinic, Regina, who has collected the clinical data used in Tables 1, 111, 1v, v, v1 and v11.

During this period 1,510 new patients with cancer of the breast were seen, the

Table IV

CANCER OF THE FEMALE BREAST
SASKATCHEWAN 1952-1959

No Treatment in Clinic (but included in total)

Reason	No.	5 Year Survival
Too advanced	30	
Too old or concurrent disease	7	I
Went elsewhere	4	3
Refused	17	3
Found at autopsy only	2	
Total	60	7

gross 5 year survival rate being 58 per cent (Table III). The majority of these patients were treated by radical mastectomy, followed by postoperative radiotherapy, where indicated, according to the policy already described. Since only cancer of the female breast is considered, II cases of cancer of the male breast are excluded. Excluded also are 17 patients who had had adequate treatment previously. The survival rate in both these latter groups is considerably above the over-all figure, which is therefore adversely affected by their omission. It should be emphasized that all cases seen are tabulated, however treated, or even if not treated, and whatever the stage. No treatment at all was given to 60 patients, 53 of whom died in less than 5 years (Table IV). Seven survived 5 years, but of these, 3 died later of disease, 1 is still alive with disease, and 3 are alive and well, having been treated elsewhere. In 2 patients the diagnosis was made at autopsy, and they are also included. Pathologic proof of disease was not obtained in 25 patients, but all except I of these died in less than 5 years. Five patients were lost to follow-up and all are counted as dead.

No apology is necessary for the use of the gross 5 year survival rate. Survival at the end of 5 years is as good an index as we have of the efficacy of treatment. Admittedly, all patients that survive this time are not free of disease, and some may suffer

from recurrence at any time thereafter, but 5 years is the commonest assessment period in malignant disease. It is a reasonable time, and, while 7, 10, or even 20 year follow-up periods may give a more exact index, the lifetime of the observer may be a limiting factor. In short, we must use a practicable generally accepted period of observation, and comparative studies based on 5 years should not be too misleading. The use of longer periods, or graphs plotting percentage survival with time, is of little value for comparison between series, and merely serves to pull the wool over the eyes of the neophyte. It is essential to use the gross rate because it is simple, and because the determination of survival is entirely objective. Deaths from all causes, or ignorance as to the fate of the patient, must be aggregated. There are too many sources of error and opportunities for manipulation of results, if "determinate" figures are used.

The exclusion of all new primary cancers of the contralateral breast represents an arbitrary decision, although the over-all results are hardly influenced thereby. The decision to call cancer of the contralateral breast a new primary tumor, rather than a secondary deposit, was made on the following grounds: (1) The tumors of both breasts must be unequivocal carcinomata, and ideally each should have intraduct carci-

Table V

CANCER OF THE FEMALE BREAST

NEW PRIMARY CANCER OF THE

CONTRALATERAL BREAST

SASKATCHEWAN 1952-1959

Interval between First and Second Cancer	No.	Survived 5 Years after Second Cancer
Simultaneous	9	5
o-ı year	7	3
1-5 years	22	12
6-10 years	4	2
Over 10 years*	15	7
Total	57	29

<sup>\*</sup> Longest interval—29 years.

Table VI

CANCER OF THE FEMALE BREAST
RESULTS OF ROUTINE TREATMENT ONLY IN OPERABLE PATIENTS

SASKATCHEWAN 1952-1959

Treatment	Description of Disease	No.	5 Year Survival	Per Cent 5 Year Survival
Radical mastectomy + or - postoperative radiotherapy	Axillary lymph nodes not involved	557	477	85.6
Radical mastectomy +postoperative radiotherapy	Axillary lymph nodes in- volved (pathologically)	592	303	51

noma demonstrable as the source of the tumor; (2) if either local recurrence or metastases of the first cancer are present, then intraduct carcinoma as the source of the new primary must be demonstrated; and (3) rarely, the two primary tumors may show distinctly different histology.

The elapsed period between the occurrence of the two primary tumors does not seem to matter too much insofar as survival after the second cancer is concerned (Table v), and it seems strange at first sight that prognosis is little affected by the double jeopardy of 2 separate cancers of the breast. It is possible, however, that there is an involuntary element of selection in the group of second primary cancers in that the more advanced cases, possibly in the presence of wide spread on the chest wall, supraclavicular lymph node involvement or distant metastases, might frequently be mistaken as examples of spread of disease to the other breast from the first cancer—a rather natural assumption. Such probable exclusions would explain the high apparent survival rate.

There were only 22 patients 30 years of age or younger in the whole group, and 12 of these survived 5 years, confirming the contention of Moore and Lewis<sup>20</sup> that prognosis is not adversely affected by youthfulness.

In the present series, radical mastectomy constituted the main primary method of treatment, supplemented sometimes by radiotherapy when the axillary lymph nodes were not involved, and almost always by postoperative radiation therapy when the axillary lymph nodes were involved. The detailed results for the patients in whom this policy was followed are presented in Table v1, but it should be pointed out that figures in this table are selected to some degree in that obviously some early cases must be treated by other methods or not even treated at all because of complicating factors such as old age or concomitant disease. The criteria of operability were not at all stringent. No limit was placed on the size of the primary tumor, and attachment to underlying muscle, or ulcerations of the skin overlying the tumor were not considered contraindications to operation. Furthermore, the separation of cases into those without pathologic evidence of disease in the axilla and those with lymph node invasion is to some extent arbitrary, since a very thorough pathologic search might well have disclosed further microscopic invasion of a few lymph nodes in some of the cases apparently without lymph node involvement. The transfer of these early examples of lymph node invasion, then, from the first group to the second, would improve the survival rate in the second group, because, as is well known, cases with early involvement of axillary lymph nodes do better than those with more advanced axillary disease. The results of the first group, moreover, will be improved by the exclusion of those cases with micro-invasion of the axillary lymph nodes. Thus

TABLE VII

CANCER OF THE FEMALE BREAST
RESULTS OF TREATMENT IN PREMENOPAUSAL
PATIENTS WITH POSITIVE AXILLARY
LYMPH NODES
SASKATCHEWAN 1952-1959

Clinic	No.	5 Year Survival	Per Cent 5 Year Survival
Saskatoon (a) Whole group (b) Sterilized only	102 71	58 47	57 66
Regina Whole group	106	57	54

we can have the peculiar effect of improving our results in both the very early and moderately early groups merely by persuading the pathologist to cut a few hundred more sections. Tables such as this can be quite misleading when compared with some other series of cases in which different methods of selection have been used. This information is included merely to serve as an illustration of the pitfalls of comparing one selected series with another in which criteria of selection are different. In spite of this clear statement, the odds are excellent that someone or other will "lift" this table and compare it with the results of treatment of "Stage 1" and "Stage 11" cases by some other method.

Routine adjuvant treatment, other than radical mastectomy and postoperative radiotherapy was not employed, with I exception. Several years ago it was decided, at one clinic, to sterilize by external radiation all premenopausal women suffering from cancer of the breast, which had been shown pathologically to have spread to the axillary lymph nodes, while using the patients in the other clinic as controls, since the composition of patient material at each clinic was likely to be similar, inasmuch as about half of the population of the province was served by each. The group, of course, is rather restricted, since menopausal and postmenopausal women were excluded.

Radiation sterilization was performed by parallel opposing fields to the pelvis, administering a central dose of 1,200 r in 4 days, usually with cobalt 60 teletherapy. The results are shown in Table VII. The two clinic groups are similar numerically and there is no significant difference in their gross 5 year survival rate. Only 71 of the 102 Saskatoon patients were sterilized, the disparity being due sometimes to the refusal on the part of the patient or referring doctor or, much more frequently, merely forgetfulness on the part of the attending physicians. It is difficult to see how any significant factors of selection could have entered into this material, but it is felt that in spite of the high survival rate of the sterilized patients, no conclusions can be drawn because the survival rate of each total group from the two clinics is similar. Perhaps the best lesson to be learned is that little information can be expected from an inadequately executed clinical experiment.

Dissatisfaction with radical mastectomy arises from either what are thought to be poor results from a curative point of view, or an alleged propensity to complications and disability. Most of those who complain of a poor survival rate following it are unable to substantiate their position by a convincing comparison of similar series of patients treated by competing methods. It is clear to all that some patients with the earliest and most localized disease will succumb however the local tumor is treated because of the biologic properties of some tumors which may metastasize even before the primary lesion is detectable by any of our present methods. We have no satisfactory means of determining which tumors, or, perhaps which hosts, fall into this category at the present time. It may be hypothesized that there are two extreme kinds of breast cancer, one which disseminates almost immediately following its inception and another which remains localized indefinitely, with a broad spectrum of tumors between these two extremes. It is this great variation in behavior in apparently histologically similar cancers that fosters the

present confusion and lack of unanimity in treatment approach. Thus almost any method of local extirpation or control will yield similar late results in the two extreme varieties—the very localized and the occultly disseminated—but there may well be a profound difference in the index of success in the intermediate group. Since we have no satisfactory means of classifying cancer according to its aggressive propensities, we are forced to treat clinically similar cases in similar ways. Suppose, however, that method A deals successfully with a large proportion of the intermediate group, whereas method B does not, then the superiority of A may not be immediately apparent in the over-all experience, because of the inadvertent inclusion of patients in, or close to, the two extreme groups where the results of treatment A and B are likely to be similar. This state of affairs predisposes to conflicting views on treatment policy. In order to clarify the situation, it is necessary to overcome the statistical uncertainties by comparing only very large series, each treated differently, in which all errors arising from case selection have been excluded. Such a comparison is possible by large planned strictly randomized experiments, and, indeed, a few have already been inaugurated. The practical and ethical difficulties in the widespread use of such experiments, in a disease in which strong preferences are often held by medical personnel involved, are, in most centers, insuperable at the present time. An alternative method of comparison is to study all of the cases of cancer of the breast arising in a circumscribed geographic region and compare the survival rate with that of another region where a different routine treatment policy has been adopted. In this way, the element of selection is entirely eliminated, since the constitution of the series is governed neither by the general type of case referred to one institution, nor by any process of selection after admission to an individual hospital or clinic. While it is desirable that the majority of the more favorable cases be treated by one particular method, it is not necessary, desirable, or even possible to treat every last patient in exactly the same way. Factors such as age of the patient, concomitant disease, local extent of the tumor, presence of distant metastases, even the wishes or refusal of the patient herself will all necessitate a departure from routine. In spite of this, all patients however treated or even if not treated at all, must be included in the series. Such criteria invalidate evidence derived from the results of treatment by one particular method when any kind of selection whatsoever enters into the constitution of a series. It is the light-hearted casual approach to the presentation of results, particularly in cancer of the breast, which has been responsible in no small measure for the present confusion. The reporting of results by "stages" of disease is uninformative because of the great variety of staging systems, because differences in interpretation occur in different centers even when the same staging system is used, and because the possibility of bias, voluntary or involuntary on the part of those performing the staging, is obvious. The use of the gross 5 year survival rate is simple and logical, as has already been pointed out. There must be no exclusion of any original primary cancer, and the determination of survival is not subject to bias. It is only in this way that objective comparison can be made.

Most of these arguments were put forward by McWhirter<sup>17,18</sup> when he reported on the benefits of treatment of cancer of the breast by simple mastectomy and postoperative radiation therapy. Unfortunately, he had no similarly unselected series, treated differently, available for comparison with his own results at that time, and there was therefore no evidence available to indicate whether the 5 year survival rate of approximately 42 per cent was good or bad. It did, however, provide a useful baseline. Although the report of McWhirter<sup>17</sup> was for the period 1941–1947, a subsequent report4 from Edinburgh would seem to indicate that this rate has

changed but little in more recent years. According to the criteria laid down by McWhirter, 17 defining the extent of coverage of the whole population of a region, the Saskatchewan series of 1945-195227 was similarly constituted, and showed a 5 year survival rate of 52 per cent, the main treatment being radical mastectomy, with postoperative radiotherapy under certain conditions. The latest 5 year survival rate in Saskatchewan, 1952–1959, is 58 per cent, and it is considered that complete centralization of the treatment of all cases occurring has been approached as closely as possible. Under the existing conditions, moreover, the few patients who are not referred to the clinics are likely to be suffering from very early disease, rather than late, and their inclusion, if this were feasible, would merely serve to improve the present survival rate. The improvement in results in later years, when a greater percentage of the cases occurring in the province has been registered—may reflect improvement in handling methods, both surgical and radiotherapeutic. There is no doubt that the average patient who develops cancer of the breast in Saskatchewan has a much greater chance of surviving 5 years than a similar patient in Southeast Scotland, and the routine use of simple mastectomy plus radiotherapy must be therefore considered as being considerably inferior to routine radical mastectomy plus radiotherapy.

Apart from this practical demonstration of the failure of simple mastectomy, there are compelling theoretic advantages in the use of the radical mastectomy, as compared with simple mastectomy or more local removal of the tumor. It is agreed that secondary deposits have a tendency to develop on the ipsilateral chest wall, but surely they should be less likely to occur when an extensive removal of tissue is performed. The addition of postoperative radiotherapy may prevent some, but not all, of these recurrences. It has been amply demonstrated that even the use of skin grafts during radical mastectomy does not

prejudice radiotherapy to the chest wall, and the benefit of the latter should be similar after either operation. With radical mastectomy plus radiotherapy, therefore, we offer the patient more hope of local control than with simple mastectomy plus radiotherapy. The same argument applies even more forcefully to the axilla. Here, as we all know, the incidence of recurrence of involved lymph nodes after radical mastectomy, reasonably well performed, is almost nil, and undoubtedly radiotherapy alone cannot compete with surgery in this respect. There is, however, no contraindication to the use of radiotherapy to the axilla after either operation, and in equal dosage, so that by the use of radiotherapy plus removal of the lymph nodes we get the best of two worlds. If occult disease has spread beyond the limits of the axillary dissection, admittedly the operation is useless in respect to the axilla or its apex, but, at least, the same benefits can be expected from postoperative radiotherapy as if the radical mastectomy had not been performed. Indeed, the removal of grossly involved lymph nodes may improve the chances of success of radiotherapy because such lymph nodes are probably less radiosensitive than smaller, and, therefore, better oxygenated ones. The contention that the process of dissection of the axillary lymph nodes may disseminate the disease is merely conjecture and would seem to be refuted by the gross results in the present series. The extension of similar arguments to the internal mammary lymph node chain would seem to be logical, providing radical surgery is feasible and not accompanied by a serious morbidity rate. The work of Urban indicates that this may be so, but it remains to be seen whether the average general surgeon can reproduce his results. Urban logically supplements his supraradical operation with postoperative supervoltage irradiation when the lymph nodes are found to be involved.

The virtue of postoperative radiation therapy is not accepted by all. Cole, and Paterson and Russell, in a randomized experiment, show that routine radiation

therapy, administered according to two separate techniques, after radical mastectomy, did not produce any better late results than radical mastectomy alone, followed by radiotherapy only when recurrence became obvious. The conclusion drawn, therefore, is that prophylactic irradiation is not more effective than irradiation restricted to those who develop local recurrence after surgery. Guttmann<sup>9</sup> and McWhirter<sup>19</sup> have shown conclusively that radiation therapy to the primary tumor and involved lymph nodes in the axilla, supraclavicular region, and internal mammary chain can be successful. We are all familiar with the apparently complete resolution of cancer of the breast, both primary and secondary, which can sometimes be produced with radiotherapy, but few would claim that such treatment alone is as effective locally as surgery, when the latter is feasible. Under these circumstances, it is hard to see why radical mastectomy with postoperative radiotherapy should not be more successful than a more conservative operation with the same postoperative radiotherapy. McWhirter<sup>19</sup> himself has said that radical mastectomy alone is superior to simple mastectomy alone. With the addition of radiotherapy to both, therefore, why should not the former still remain superior? The report from Copenhagen<sup>12</sup> comparing the results of treatment by simple mastectomy and postoperative radiotherapy with those produced by extended radical operation alone is hardly pertinent to this argument, since radical mastectomy with postoperative radiotherapy has not been employed.

Radical mastectomy has been reviled because of the high alleged incidence of complications and disfigurement. The loss of the breast alone, whether by simple or radical mastectomy, is said to have a profound detrimental psychologic influence on the patient. To my mind, such a result is minimized by informing the patient prior to surgery what is going to take place, should the frozen section be positive, and in adopting the attitude, without emphasis, that this is the normal course of events. If well intentioned thorough investigations as to the attitudes and reactions of the patient prior to, and after, the operation are conducted, undoubtedly evidence of psychologic trauma will frequently be manifest. Such evidence, however, will usually have been produced by the inquiry rather than disclosed by it. The adoption of a casual attitude by the doctor before the operation and throughout follow-up examinations will go a long way towards eliminating these untoward and unnecessary occurrences.

The physical handicaps following radical mastectomy have been overemphasized by those advocating other methods of treatment. Great play is made of the edema and interference with the use of the arm on the affected side. Just how serious are these criticisms? We have previously reported a retrospective study of 590 patients,28 each of whom had had a radical mastectomy any time in the past, and who were seen consecutively in follow-up at the Saskatoon Cancer Clinic during the course of I year. Any increase in size of the arm, either 10 cm. below the acromial process, the forearm, or the wrist, when compared with the measurements of the arm on the unaffected side was considered as "swelling." Almost 70 per cent exhibited some increased circumference of the arm on the side of the operation, but it was great in only a few. A further group of 100 normal women in about the same age range was similarly measured, and considerable differences were found between the measurements of the two arms of many individuals, although the women themselves were unaware of this disparity. The right arm was frequently thicker than the left. The average increase in circumferences compared with differences between the arms of normal individuals is listed in Table vIII and it will be noted that these changes are surprisingly small. A more important consideration is the impairment of function. Most patients (65 per cent) stated that their arm movements were normal and only 2 per cent had severe impairment of function. Strangely,

TABLE VIII

DIFFERENCE IN UPPER ARM CIRCUMFERENCES IN 590 MASTECTOMY PATIENTS COMPARED WITH SIMILAR MEASUREMENTS IN 100 CONTROLS

Group	Mean of Differences between Arms (cm.)	"t" Test*
Right mastectomy	I -44	Significant
Control	0.59	Significant
Left mastectomy	0.94	Significant
Control	0.59	Significant

<sup>\*</sup> To 5% confidence level.

there was no relation between swelling of the arm and dysfunction—a woman with a swollen arm was no more likely to have impaired function than a woman with an arm of normal measurement. The occurrence of swelling or dysfunction was not related to lack of formal exercises immediately after the operation, the interval since operation, method of drainage of the wound, skin grafting, or obesity. Those, however, who had positive axillary lymph nodes and who, therefore, almost always had postoperative radiotherapy did have an increased incidence of both swelling and dysfunction. When a large number of patients is considered, those with serious physical handicaps are small in number. Despite a general impression to the contrary, a 12 per cent incidence of edema of the arm has been reported by Bruce and Tough<sup>4</sup> from Edinburgh following simple mastectomy and postoperative radiation therapy. Unfortunately, the criteria for recognizing "edema" are not stated.

The timing of sterilization in the management of operable cases is a controversial matter. In the Saskatchewan series, only a small well-defined group of premenopausal patients received radiation sterilization as part of the initial management, and no clear-cut evidence of statistical improvement was obtained. It is undoubted that oophorectomy and radiation sterilization

can profoundly influence the course of the disease in premenopausal, menopausal, and some postmenopausal women, but should it not be reserved for recurrent or very advanced cases? The statistical evidence from Manchester<sup>21</sup> manifestly indicates that younger women, up to 2 years postmenopausal, have a higher 5 year survival rate if radiation sterilization forms part of the initial treatment. On the other hand, Kennedy et al.18 have shown that, in similar groups of patients, 5 year survival rates are the same whether the sterilization is part of the original treatment or whether it is reserved until recurrence or metastasis takes place. If the latter view is correct, then some patients, who do not develop metastasis or recurrence are saved sterilization, and, in the absence of a large bulk of evidence to the contrary, this would seem to be the sensible course to follow at the present time.

#### SUMMARY

It is emphasized that, while early diagnosis does not necessarily guarantee lack of dissemination of the disease, prompt treatment is of great importance in many patients. Until it can be conclusively proven in a large series of entirely unselected patients that less comprehensive methods of treatment are superior, radical mastectomy in conjunction with postoperative radiotherapy must be considered the best treatment in early "operable" cases. The experience of Saskatchewan's centralized cancer program, which covers in a purely voluntary way almost all cancer occurring in the province from all strata of society and in which a clear, consistent treatment policy has been maintained, attests the validity of this contention. It is possible that more radical operations, again with radiotherapy, may be even more successful, but certainly, in the light of present evidence, patients who are not energetically managed are getting something less than the best.

The Ontario Cancer Foundation London Clinic Victoria Hospital London, Ontario, Canada

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# ROLE OF SUPERVOLTAGE IRRADIATION OF REGIONAL LYMPH NODE BEARING AREAS IN BREAST CANCER\*

By RUTH J. GUTTMANN, M.D. NEW YORK, NEW YORK

THE question has often been raised whether it is possible to sterilize carcinomatous lymph nodes with irradiation and to increase the life span of the patient with this procedure. I have always felt very strongly in the affirmative and have invariably emphasized the need for postoperative irradiation of lymph node bearing areas after a radical mastectomy, especially when the histologic examination of the specimen has shown a large number of involved lymph nodes. Since, however, the accuracy of clinical observations is often difficult to prove I have studied the effect of radiation on metastatic lymph nodes of various primary diseases by microscopic examination of these lymph nodes before and after irradiation, in order to determine the effectiveness of the method.

The most important findings of this study were the following: It is possible to destroy metastatic disease in lymph nodes with a high dose of radiation, i.e., a minimal tumor dose of 5,000 rads, delivered in 5 weeks time with a megavolt unit. The size of the involved lymph nodes has a definite bearing on the prospect of destroying the tumor completely; the larger the size of the lymph node, the less the chances of sterilization. We have found that lymph nodes below 3 cm. in diameter can be controlled, while good results become increasingly difficult with increasing size.

In this paper the role of supervoltage therapy in the management of regional lymph node metastases from primary carcinoma of the breast in 3 different situations is reported.

First is a group of patients who had undergone radical mastectomy and who were referred for the treatment of internal mammary lymph node metastases after an interval of several months, or years. The second group represents patients who underwent radical mastectomy and were referred for postoperative irradiation of extensive disease in the axillary lymph nodes. The third group consists of patients whose biopsies—as practiced by Haagensen —showed a primary operable breast tumor and metastases of the internal mammary lymph nodes and/or lymph nodes in the apex of the axilla, and whose only therapy consisted of irradiation because at least one of these regional lymph nodes had been found to be positive.

It is obvious that the first group, where there was visual evidence and sometimes microscopic proof of the disease, and the third group, where there was always histologic proof of the disease, lend themselves best to an evaluation of the achievements of external megavolt irradiation, while the proof of the effectiveness of radiotherapy in the second group, where irradiation was considered to be "prophylactic," is more difficult to establish.

Figures 1 through 4 are photographs made before, and 6 and 8 years after irradiation showing visual proof of the effect of irradiation on internal mammary lymph node metastases. Quite a number of these patients have been seen at the Francis Delafield Hospital in New York and a group of 20 who were treated in the Department of Radiotherapy was evaluated. The dosage

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<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965. From the Department of Radiotherapy, Francis Delafield Hospital, College of Physicians and Surgeons, Columbia University, Columbia Presbyterian Medical Center, New York, New York,

which we have found to be effective in the sterilization of such metastatic lymph nodes is a total tumor dose of 5,000 or 6,000 rads, depending on the individual tolerance, delivered in 5 or 6 weeks time. The therapy is given with a 2 million volt roentgen-ray unit, with a half value layer of 7 mm. of lead and a target skin distance of 100 cm.

Six of the 20 patients who have been treated in the described fashion are alive from 5 to 8 years. The others died of generalized metastases which already had been present at the time of their referral for treatment of the internal mammary lymph node metastases. The number of treated patients is small and does not permit any statistically valid figures, but there is no doubt that localized metastatic disease to the internal mammary lymph nodes can be sterilized with an adequate dosage of radiation and that long survival can be achieved.

In the second group of patients, in whom a radical mastectomy had been performed and massive axillary disease had been found and in whom postoperative radiotherapy had been decided upon, the evaluation of treatment results is very difficult. The extent of the lymph node spread and, therefore, the stage of the disease are not



Fig. 1. Metastasis to the internal mammary lymph nodes from primary carcinoma of the breast.

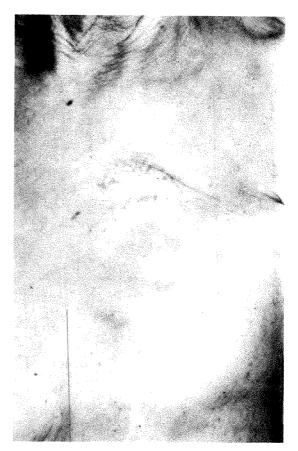


Fig. 2. Same case as in Figure 1, 6 years after irradiation.

known and a stage by stage comparison cannot be made in these patients referred from other hospitals.

Various centers have treated a comparable series of patients with axillary metastases after radical mastectomy, with and without postoperative irradiation, in the attempt to arrive at a conclusive answer. An increase of 5 to 10 per cent in the 5 year survival rate has been reported in the groups which received postoperative radiotherapy. These results were often coupled with the statement that "patients with somewhat more extensive disease received radiotherapy," which would indicate that the number of patients with a survival period of 5 years might have been greater. Even if we accept the fact that only 5 out of 100 patients show an increase in their 5 year survival chances, the procedure has



Fig. 3. Metastasis to the internal mammary lymph nodes from primary carcinoma of the breast.

proved its value, especially if no serious side effects are connected with this combined treatment approach.

At the Francis Delafield Hospital, we have not been able to run any such comparable series. Our patients undergo multiple lymph node biopsies before the method of treatment is determined, and it is therefore rather rare that a patient is treated postoperatively because of unexpected involvement of the high axillary lymph nodes. We do have a large number of patients who had been operated upon elsewhere and who were sent to us for postoperative radiotherapy, but such patients do not lend themselves to a systematic study. Too often, there was no staging of the disease before surgery was performed. Another factor is the variety of surgical procedures which were carried out and which often are not comparable, although all are classified as "radical mastectomy."

In the third group of patients, which is unique to the Francis Delafield Hospital, the most significant answer to the question of the role and importance of irradiation in regional lymph node metastases has been found. These are the patients with clinically operable carcinoma of the breast, where biopsies of the regional lymph nodes have shown metastatic disease in any one of the lymph nodes of the apex of the axilla or of the internal mammary chain. No surgery

had been offered to these patients for it is felt that the disease in such cases has extended beyond the reach of surgery. Here, radiotherapy was the sole method of treatment.

The treatment approach in these patients has been described before. Briefly, a total minimal tumor dose of 5,000 rads, delivered in 5 weeks time, given with a 2 million volt unit, directed to the breast proper and to all of the lymph node bearing areas was given. The primary tumor was treated with an additional tumor dose of about 2,000 rads in 2 weeks time.

At present, 168 patients have been evaluated and followed over 3 years, 148 patients over 4 years and 123 patients over 5 years. Table I shows the distribution of the disease in the distant regional lymph nodes. Probably a greater number of patients than the ones shown in this table has had disease in the internal mammary lymph nodes and apex of the axilla, but triple biopsies are not made routinely any more.

Table II shows the results in the treatment of these patients. The 3 and 4 year survival is 70 per cent, the 5 year survival is 52 per cent, the 7 year survival is 40 per cent and the 10 year survival is 33 per cent. It is interesting to note that 6 of the patients who had survived more than 5 years have died not from their primary disease, but from other causes, and that autopsies

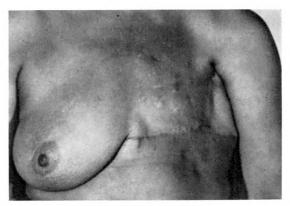


Fig. 4. Same case as in Figure 3, 8 years after irradiation.

TABLE I
DISTRIBUTION OF INVOLVED LYMPH NODES

Year	No. of Patients	Involvement of Internal Mammary Lymph Nodes and Apex of Axilla	Involvement of Internal Mammary Lymph Nodes	Involvement of Apex of Axilla
April, 1952-53	6	4	· I	I
April, 1953-54	10	8	I	1
April, 1954-55	16	IO	4	2
April, 1955-56	16	.8	5	3
April, 1956-57	19	9 -	7	3
April, 1957-58	33	6	12	15
April, 1958-59	16	5	5	6
April, 1959-60	13	4	4	5
April, 1960-61	15	I	11	3
April, 1961-62	24	5	9	10
	<u>—</u>	<del>-</del>		THE CONTRACTOR OF THE CONTRACT
	168	60	59	49

showed residual disease only in I of these patients; nevertheless, the patients are included in the deaths due to cancer.

These survival results were possible only when irradiation had succeeded in destroying the primary tumor and the metastases in the lymph nodes which had been proved to be positive. The conclusion from these survival figures is strengthened by the fact that autopsy showed no evidence of disease in 14 patients, while 3 other patients who died from their disease had no evidence of disease in the treated breast and lymph node bearing areas. It is pointed out here that the disease in these patients is char-

acterized by a tendency to early and rapid spread as documented by positive distant regional lymph node biopsies, in spite of the limited size of the primary tumor. These patients had disease which widely metastasized and such grave prognostic findings will definitely influence the outcome of the untreated disease unfavorably. Such patients are not found as survivors in a group of untreated patients and, therefore, it is concluded that any long survivals in this group are the result of the radiation therapy. The value of adequate dosages of radiation and their ability to sterilize metastatic lymph nodes are stressed.

Table II

FOLLOW-UP OF PATIENTS TREATED BY RADIOTHERAPY

Followed	Total No. of Patients Treated between 1952–1961	Alive	Remarks
3 ýears	168	124=70%	· ·
4 years	148	102 = 69%	•
5 years	123	64 = 52%	
6 years	110	48 = 45%	6 patients died between 6 and
7 years	98	39=40%	10 years of other causes than
8 years	65	20=31%	their primary disease—at au-
9 years	46	14=32%	topsy only I showed residual
10 years	30	9=33%	carcinoma.

#### SUMMARY

It is shown that definitive radiotherapy with megavolt irradiation is capable of destroying metastatic disease in regional lymph nodes in various patient groups with proved metastatic carcinoma in such lymph nodes.

Radiotherapy to large metastatic internal mammary lymph nodes, which had appeared after radical mastectomy, has kept 6 out of 20 patients alive for more than 5 years. Postoperative radiotherapy has, as reported in the literature, increased the number of patients who have survived 5 years by 5 to 10 per cent—a figure which we feel is significant.

In a series of cases receiving radiotherapy as the exclusive treatment for carcinoma of the breast with microscopically proved distant lymph node metastases, 52 per cent of the patients lived for 5 years. In addition, a number of patients who came to autopsy showed no evidence of disease anywhere in the body, and in others no residual disease in previously treated lymph nodes was found. This appears to verify the clinical findings and observations; namely, that megavolt irradiation has an undisputable place in the management of patients with metastatic disease from primary carcinoma of the breast.

Department of Radiotherapy Francis Delafield Hospital New York, New York

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# THE ETIOLOGY OF TREATMENT FAILURES IN EARLY STAGE CARCINOMA OF THE CERVIX\*

By RALPH M. SCOTT, M.D., HERBERT E. BRIZEL, M.D.,†
and CRAIG WETZELBERGER, M.D.;
LOUISVILLE, KENTUCKY

EARLY cancer of the uterine cervix is recognized as one of the most favorable situations confronting the radiotherapist. Cure rates as high as 90 per cent in Stage 1 and 70 per cent in Stage 11 are being reported. Successful treatment being the rule rather than the exception suggests that the best approach for improving cure rates might be a critical analysis of the failures.

Total extent of disease can explain a great number of failures in Stage III and Stage IV carcinoma. Radioresistance is often blamed for the small but significant number of failures in the earlier stages, but this is not well documented. Unrecognized extension of disease, mistakes in judgment on the part of the radiotherapist and many other factors are often involved. Radiocurability and radiosensitivity are not synonymous and to arbitrarily blame radioresistance for a significant number of failures in early stage cancer does not seem justified.

In a relatively small series of Stage I carcinomas of the cervix treated solely by irradiation, we have attempted to analyze various factors in the survivals as opposed to the failures regarding accuracy of staging, histologic picture of the tumor, general condition of the patient, hematologic and urologic factors, and dosimetry in an effort to clarify the problem. To us it seems that the extrinsic influence of these factors on the tumors, either alone or in combination, is much more likely to result in a poor response to radiation than true intrinsic radioresistance on the part of the tumor.

#### CASE MATERIAL

A total of 56 Stage 1 cases was analyzed: 36 were 5 year or longer cures and 20 were failures. The disproportionally high number of unsuccessful cases is accounted for by the fact that failures were selected for investigation up to the time of analysis, but the cures were only those cases with a 5 year or longer follow-up. Difficulties in the project become quite apparent because of the relatively small number of cases in both groups, the number of uncontrolled variables involved and the problems involved in retrieval of data from old charts in a retrospective study. Since we are not dealing with large homogeneous groupings, a statistical analysis seems worthless. With these limitations in mind, we have examined our material looking only for gross differences in the 2 groups.

#### STAGING

Accurate staging, as well as having prognostic significance, is essential in treatment planning. It is often difficult to be certain whether parametrial induration represents tumor, inflammation or a combination of both. To assure proper therapy, we assume that it represents tumor spread, but in evaluating treatment results, where there is any doubt regarding staging, it is understood that the lower of the 2 stages should be chosen. Graham et al.<sup>6</sup> have shown in a large collected series of nonirradiated operated cases that 16 per cent of clinically Stage I carcinomas of the cervix have metastasized to pelvic lymph nodes. This un-

‡ Clinical Fellow of The American Cancer Society.

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<sup>†</sup> Advanced Clinical Fellow of The American Cancer Society.

detected extension of disease certainly accounts for some therapeutic failures. Ancillary studies such as intravenous pyelography, lymphography, isotope renography and cystoscopy should reduce the number of relatively advanced carcinomas which are wrongly classified as Stage I lesions. Only an experienced examiner should have the final decision as to the allocation of a lesion into the particular stage and, if necessary, bimanual examination under general anesthesia should be performed.

The final decision as to staging in our cases was made by a senior staff gynecologist in almost every case, but a review of the charts reveals that the anatomic description of the disease was at variance with the final staging in some instances. This would seem to indicate compliance with the rules of staging. It is interesting, if not significant, that 20 per cent (4 of 20) of the failures and only 8 per cent (3 of 36) of the cures presented some question as to being understaged.

#### GRADING AND HISTOLOGY

Most authorities<sup>1,2</sup> have not been able to definitely correlate survival in cancer of the cervix with histologic grading, Glucksman et al. being a notable exception. Indirectly, however, there probably is some relationship between grading and survival because the more anaplastic tumors tend to be of advanced stage when diagnosed. Careful histologic examination may prove of some benefit since one series has shown that 63 per cent of the patients showing intralymphatic tumor in a biopsy of the cervix have ultimately demonstrated positive pelvic lymph nodes.6 Likewise, more knowledge of the nature of microinvasive carcinoma must be accumulated regarding its natural history and therapy.

The microscopic slides on 18 of the 20 failures and 29 of the 36 cures were available and were reviewed by our senior pathologist. All of the sections were reviewed whenever a conization was performed. Microinvasive cancers and occult invasive

lesions were found in both groups. Of the failures, II per cent (2 of 18) were microinvasive while in the cures 20 per cent (6 of 29) fell into this category. Both groups contained II per cent occult invasive lesions (2 of 18 failures and 5 of 29 cures). Systematic grading was not done, but the remainder of the cases, both the successfully treated and the failures, were, except for 3 keratinizing lesions, poorly or only moderately differentiated invasive lesions. Thus, it is felt that there was little if any significant histopathologic difference in the 2 groups.

#### GENERAL CONDITION

Associated conditions such as hypertensive cardiovascular disease, diabetes, obesity, malnutrition and chronic weight loss can play a role in the ultimate patient response to therapy regarding either the initial treatment planning or perhaps as an associated factor in the response to treatment. Pelvic infection is also an important consideration in the same respect. This may be due to parametrial and/or adnexal infection secondary to gonorrhea or simply a local inflammatory response to the tumor itself in and around the cervix, fundus and paracervical region. With the exception of pelvic infection, the previously mentioned categories of general condition have not received much attention regarding their relationship to therapeutic response, undoubtedly because of the difficulty in evaluating these factors. In a retrospective study, decisions regarding general condition are very difficult to make and can be only qualitative at best. After careful consideration, we classified 65 per cent (13 of 20) of the failures as being in less than optimal general condition while only 22 per cent (8 of 36) of the cures were so classified.

#### FEVER

Fever may be due to previously present urinary tract disease, endometritis, pelvic inflammatory disease, or simply the result of the cervical, uterine and urinary tract instrumentation and manipulation involved in the diagnostic work-up or radium insertion. In many instances, no specific cause can be determined. Whatever the cause, local inflammatory factors can influence the therapeutic result. Van Herik<sup>9</sup> found that the longer the duration of the fever, the worse the prognosis and that the incidence of fever increased with the degree of advanced staging of the disease. Whether or not this is statistically significant in Stage I cases is not completely apparent however.

Of the patients in our series who had at least one intracavitary radium application, 64 per cent (9 of 14) of the failures and only 17 per cent (5 of 29) of the cured patients developed a fever of greater than 100° F. orally. Interestingly, 8 of the 9 patients in the failure group who exhibited fever during the radium application were classified as being in poor general condition. It was also noted that as the general condition of the cured cases improved there was considerably less febrile response.

#### HEMATOLOGIC PICTURE

It has been well demonstrated that oxygenation of tumor tissue plays an important role in radiosensitivity. Garcia<sup>5</sup> defined anemia as less than II gm. per cent hemoglobin and found significantly poorer radiotherapeutic results in all stages when the patient's level was below this figure. In a series by Evans and Bergsjö, however, anemia did not create a significant difference in survival in Stage I cases. They postulated that the role of oxygenation was more significant in the more bulky later stage disease. Using 11 gm. per cent hemoglobin as a dividing line, 10 per cent (2 of 20) of the failures and 5 per cent (2 of 36) of the cures were below this figure prior to radiotherapy. One would expect the hematologic picture to be relatively good in Stage I lesions as compared with the later stage cases although some patients in both groups presented with profound anemia

and required pretreatment transfusions. We found no difference in the results of treatment relative to whether the patients required transfusions beforehand.

#### URINARY TRACT COMPLICATIONS

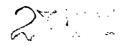
It is well known that the prognosis is ominous when there are pyelographic changes, particularly those due to obstruction. Garcia<sup>5</sup> found that the salvage was significantly lowered when uropathy was present, even taking into account disparities in staging. However, these urinary tract complications are not as significant in Stage I disease as in the more advanced stages.

Practically all patients in both our groups had intravenous pyelograms, routine urinalysis and cystoscopy prior to irradiation. No significant abnormalities were found in either of the treatment groups in this study.

#### SEROLOGY

It is fairly easy to speculate on the effect that gonorrheal salpingitis and pelvic inflammatory disease might have on the radiotherapeutic response, but the problem of syphilis and its effect on radiation response has received little study and is not as easy to evaluate. The problem is compounded because of the fact that gonorrhea and syphilis may be associated diseases.

The most common site of primary chancre in the female is in the vaginal fornix and cervix. It is interesting, at least, to speculate on whether this may ultimately lead to tissue changes in and around the cervix or in the paracervical structures which might influence the radiobiologic effect of the treatment. Primary syphilis probably is rather innocuous in this regard but tertiary syphilis with its fibrotic and granulomatous changes possibly could affect the radiation response. One might also speculate on possible humoral mechanisms set up secondary to the leutic process even if



there were no histologically demonstrated local changes.

In our failure group 30 per cent (6 of 20) had positive serologies while in the cure group approximately 6 per cent (2 of 36) showed a similar picture. Of the 2 cures and 6 failures with positive serologies, all were diagnosed as late latent syphilis at the time of irradiation and all were considered to have been adequately treated at sometime in the past.

#### DOSIMETRY

This is an extremely complex situation and is much more involved than a simple calculation of milligram hours based on empiric knowledge or the apparently more intricate calculations of rads or roentgens delivered to Point A. Many variables may be and usually are present. The height of the radium application within the pelvis may definitely affect the dose to the iliac lymph nodes. The relationship of the intrauterine radium and vaginal radium can be quite critical and it has also been shown that the anterior or posterior lip of the cervix may definitely receive a significantly low dose if the radium is improperly applied, in spite of an adequate dose laterally. Whether or not external irradiation is administered, and its time-dose relationship, may also be critical, even in Stage I disease, Paterson's work notwithstanding. Lateral symmetry of the application likewise can be quite important since one may have a relatively uneven dose to the right and left sides of the broad ligament if there is associated malposition of the uterus and paracervical structures. Sherman,8 in a series of 422 cases of Stage 1, Stage II, and Stage III carcinoma of the cervix, found 18 central recurrences which conceivably could have been attributed to "radioresistance." In all instances, fault could be found with the radium application with areas of low dosage. It seems certain that this experience is not unique.

Retrospective analysis of the technique of radium insertion is extremely difficult and the fact that many of the old localization roentgenograms were unavailable to us rendered it more so. Therefore, it should be understood that the analysis in this area is far from satisfactory and in many instances represents the dose as expressed in the treatment chart. This was assayed in accordance with our present day standards and any case receiving less than 6,500 rads to Point A was considered undertreated. It was surprising to us to find that approximately 50 per cent (9 of 20 failures and 19 of 36 cures) received what we would consider underdosage. Eight of the 20 failures had central recurrences and 5 of these received what we considered to be suboptimal treatment. Two other cases had pelvic recurrences without evidence of central disease. In these last 2 cases, one cannot rule out the fact that central microscopic tumor was still present, and I of these cases received a low dose of radiation.

#### MISCELLANEOUS FACTORS

In every series of cases, many factors aside from failure to control local disease tend to lower survival rates. In our study 2 cases died of distant metastases without evidence of pelvic disease. Three were lost to follow-up at varying intervals after their treatment, but 2 of these were not treated for cure because of poor general condition. The third case was lost at 54 months after apparent tumor free follow-up. Another case not treated for cure is known to have died of cancer. Five died of intercurrent disease without evidence of carcinoma in the pelvis at the time of death, I at 6 months, I at 8 months, I at 24 months, and 2 at 30 months. Another of the case failures had recurrence at 3 years, was retreated by irradiation and died 6 years later, free of cancer. None of these cases would seem to be failures due to radioresistance.

#### SUMMARY

In a small series such as this, we have obviously not been able to find an absolute or compelling reason for some treatment failures of localized cervical carcinoma with irradiation. In a strictly qualitative sense, we feel that there is at least indication that there were many more unfavorable factors operating in the failures than in the successfully treated cases. The study indicates that much more work might be done in analyzing the many variables involved in the radiotherapeutic approach to this disease from the clinical point of view before one attributes failures to some easily accepted escape phrase such as "radioresistance."

Ralph M. Scott, M.D.
Department of Radiology
University of Louisville
School of Medicine
Louisville, Kentucky 40202

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# A VAGINAL COBALT 60 APPLICATOR FOR INTRAVAGINAL IRRADIATION\*

By IRVING M. ARIEL, M.D., F.A.C.S. NEW YORK, NEW YORK

INTRAVAGINAL irradiation is a proved method for delivering radiation to cancer of the vagina and contiguous tissues. In this report a vaginal cobalt 60 applicator designed for the administration of irradiation post-hysterectomy for cancer of the uterus and in the treatment of intravaginal cancerous recurrences and metastases is described.

# DESIGN OF THE TRIOVOID APPLICATOR (VAGINAL COBALT 60 APPLICATOR)

The cobalt 60 vaginal colpostat is an expanding ovoid applicator consisting of 3 ovoids each containing cobalt 60, and is a modification of the Ter-Pogossian ovoid applicator (Fig. 1, A, B and C). After insertion of the colpostat, as the external handle is turned the ovoids spread apart to fill the vagina and expand its walls (Fig. 2, A and B). The expansivity of the ovoids is dependent upon the size and diameter of the vagina; therefore, if the region is small the applicator cannot be completely expanded. A square of saran-wrap placed in the introitus before inserting the applicator forms a protective sheath about the applicator as it is inserted into the vagina.

The ovoids contain the radioactive cobalt wires. Radioactive Co<sup>60</sup> has a gamma ray emission of 1.19 and 1.33 mev., and a beta ray emission of 0.3 mev. In Figure 3, source A consists of 64.6 mc of cobalt wire, an active length of 0.8 cm., with 0.5 mm. steel filtration. Sources B and C contain 49.3 mc of Co<sup>60</sup>, 0.6 cm. active length, with 0.5 mm. steel filtration.

The ovoids are made of nylon and are 12.5 mm. in diameter, 32.0 mm. in length with an internal capacity of 4.0×20.0 mm. The sidewall filtration is 1.5 mm. of brass and each distal cap filtration is 5.0 mm. of steel. The Co<sup>60</sup> is sealed within the ovoids;

the seal can be readily broken in case of radiation decay wherein additional cobalt 60 is needed to adjust the dosage.

The applicator is designed to deliver an initial total dose of 200 mc Co<sup>60</sup> per hr. or 310 mg. per hr. radium equivalent. Inasmuch as Co<sup>60</sup> has a half-life of 5.3 years, it is computed that there is a 1.0 per cent decay per month. Therefore, after 5 years of use, the delivery of radiation from the applicator equals 186 mg. hr. radium equivalent per hour. The applicator is recharged with 80 mc Co<sup>60</sup>, and once again delivers 310 mg. hr. radium equivalent per hour.

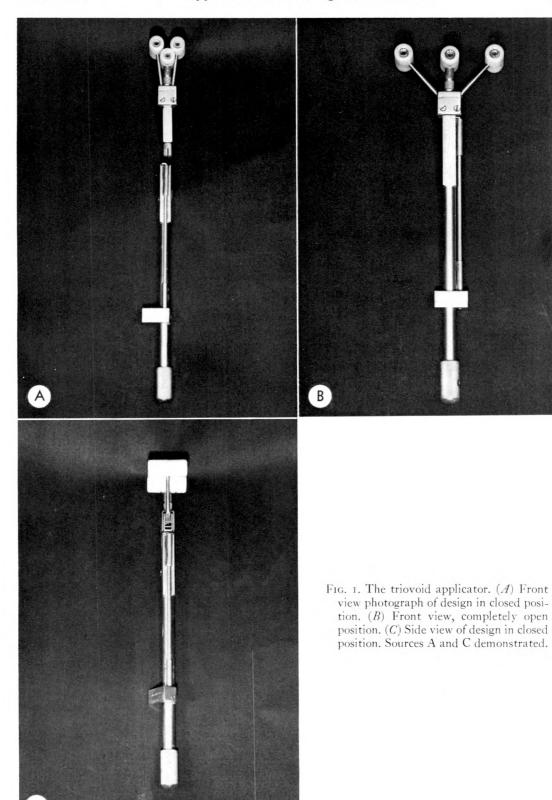
The isodose curves, kindly prepared by Morris Hodara, M.S.,\* are illustrated in Figure 3. With the applicator closed, 1,000 r/hr. is delivered to 1 cm. about the applicator; at 2.5 cm. expansion, 300 r/hr. is delivered. When the applicator is completely open, the isodose curve flattens out; whereas 600 r/hr. is delivered in the vicinity of Point A, the falloff is rather rapid and 100 r/hr. is delivered at approximately 4 cm. distance. An isodose curve between the above two is obtained with the applicator in the half open position, encountered in the atrophic, inelastic vagina which will not accommodate the fully expanded colpostat.

#### DISCUSSION

Numerous vaginal applicators have been designed in the treatment of cancer of the vagina, cervix and body of the uterus, for use either alone or in conjunction with a tandem or other radiation source within the corpus uteri. The Ernst, 2.7 the Neary, 7 and the Nolan applicators 6.7 were designed for the treatment of carcinoma of the uterine cervix. Similarly, various applicators have

<sup>\*</sup> Radiologic Physicist, Department of Radiation Therapy, St. Luke's Hospital, New York, New York.

<sup>\*</sup> From the Pack Medical Foundation, Inc., and the Radioactive Isotope Division, Hospital for Joint Diseases, New York, New York. Assisted by a grant in aid from the Janet K. Heatherington Memorial Cancer Research Fund.



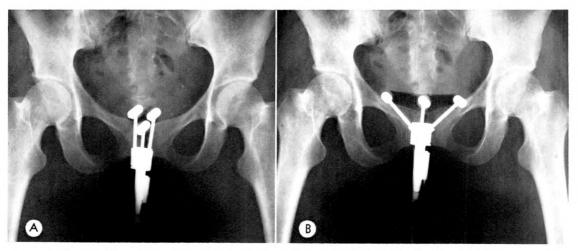


Fig. 2. Roentgenograms demonstrating intravaginal insertion of triovoid applicator.

(A) Closed position. (B) Completely open position.

been designed for the intravaginal administration of irradiation in the treatment of carcinoma of the body of the uterus, including the Stockholm boxes, the Paris corks, the Manchester ovoids and the Silverstone colpostat. 8,10 Each has its advantage and disadvantage, and may be used either alone or in conjunction with other intrauterine irradiation.

The triovoid applicator was fashioned for use by the author's surgical associates in the treatment of those patients not having received preoperative irradiation and, therefore, to provide postoperative irradiation to the vagina following hysterectomy for cancer of the cervix and/or uterine body.

In the design, we also had in mind its use in the treatment of vaginal recurrences after treatment for cancer of the uterus. That it has been successful is demonstrated in the good response obtained in the treatment of local recurrences. It is difficult to evaluate the benefit derived, if any, from its use during the postoperative period.

The great advantage of our applicator lies in the intravaginal application of irradiation easily administered on an outpatient basis. The average course has consisted of 3,000 mg. hr. radium equivalent delivered usually in 2 or 3 weekly intervals. Therefore, a dosage of 1,500 mg. hr., which usually requires 5 hours of intravaginal application, has been found satisfactory from the

standpoint of the patient's tolerance as well as of tissue reaction. If the patient had received previous irradiation, dependent upon the dosage given, the present dosage is limited to an amount varying from 1,000–2,000 mg. hr. radium equivalent.

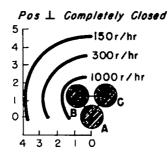
The inherent expansibility of the applicator permits irradiation of the fornices and the mid-section of the vagina; we have not had unfavorable radiation reactions in either the bladder or the rectum.

The reports in the literature indicate a somewhat better 5 year survival rate for cancer of the cervix wherein surgery is followed by radiation therapy. Thus, Lindgren<sup>5</sup> reports a 76.1 per cent 5 year survival rate. In contrast are the reports of Johnson and Haynes<sup>4</sup> who report a 58.2 per cent 5 year survival rate, and Pentecost and Brack<sup>9</sup> who report a 61.5 per cent 5 year survival rate. However, Bastiaanse<sup>1</sup> reports a 70 per cent 5 year survival rate.

#### CONCLUSION

The postoperative administration of irradiation using the vaginal applicator is a safe method and, in all probability, does destroy that cancer located within the immediate center of the applicator. However, the rapid falloff as demonstrated by the isodose curves, precludes this technique as an effective method for treating cancer at any distance from the site of the immediate vagina. For example (Pos. 4, Fig. 3), with

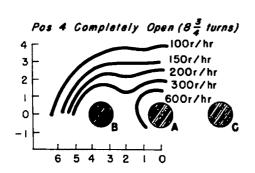
#### Co 60 APPLICATOR



#### Source

 $A=64.6\,mc$  , 0.8 cm active length  $\frac{1}{2}$  mm It.  $B=49.3\,mc$  , 0.6 cm active length  $\frac{1}{2}$  mm It.  $C=49.3\,mc$  , 0.6 cm active length  $\frac{1}{2}$  mm It.

5/1/60



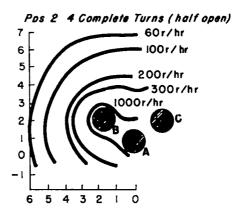


Fig. 3. Isodose curves demonstrating amount of intravaginal irradiation delivered by Co<sup>60</sup> ovoids at various expansile positions.

the colpostat completely open, therefore, at Point A, considered 2 cm. lateral to the midline and used to designate the paracervical triangles, the approximate dosage of internal irradiation delivered would be 150 r/hr., in contrast to 600 r/hr. obtained in the immediate vicinity of the central ovoid.

The described triovoid applicator has been used in a series of more than 100 patients. The over-all results were satisfactory and will be presented in a subsequent report.

Pack Medical Foundation, Inc. 139 East 36th Street New York 16, New York

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## SQUAMOUS CELL CARCINOMAS OF THE TONSILLAR AREA AND PALATINE ARCH\*

By GILBERT H. FLETCHER, M.D., and ROBERT D. LINDBERG, M.D. HOUSTON, TEXAS

THE tonsillar area is composed of the pillars and tonsillar fossa, and the palatine arch is made of the soft palate and anterior faucial pillars.

The squamous cell carcinomas originating on these anatomic structures constitute an important group of cancers, being, with those of the laryngopharnyx, the most common lesions of the upper respiratory and digestive tract. A review of the results in the world literature up to the early 1950's shows that the outlook for patients with such cancer was grim.4,16 At that time the main cause of death was failure to control local disease and regional metastases.4 Furthermore, in contradistinction to the oral cavity, where systematic policies of treatment had already evolved in the 1920's for the management of the primary lesions and neck lymph nodes, no policies of treatment had evolved for the management of the tonsillar area.

The disease is most common in patients between the age of 50 to 79 years with no difference between anatomic structures. In our material males were affected 5 times more frequently than females. There is a high proportion of severe alcoholism, mostly in female patients.

Patients with squamous cell carcinomas on the palatine arch have a diffuse metaplasia of the mucous membrane of the upper respiratory tract. It is not uncommon that multiple positive biopsies are obtained from lesions which are not grossly contiguous. Queyrat's erythroplasia, a precancerous lesion, is a diffuse red hyperplasia often seen on the palatine arch.<sup>14</sup> The original management must be planned accordingly and follow-up examinations geared to detect early subsequent primary lesions.

The purpose of the authors is to consolidate the data which have evolved on the modern radiotherapeutic and surgical management of those lesions. Therefore, only the patients treated with megavoltage equipment, which for the first time has made it possible to deliver adequate tumor doses, will be discussed.

The mucoepidermoid carcinomas, rare tumors of ectopic salivary gland origin, are best managed surgically and the lymphomas seen occasionally in the tonsillar fossa are treated with a different range of tumor doses, and will not be discussed here.

Because of differences in clinical behavior, the following anatomic sites will be discussed separately: retromolar trigone, anterior faucial pillar, glossopalatine sulcus, soft palate, tonsillar fossa, and posterior faucial pillar.

#### STAGING OF DISEASE

Staging of the primary lesion and the lymph node metastases has been as follows:

- T<sub>1</sub>—Tumors less than 3 cm. in diame-
- T<sub>2</sub>—Tumors 3 to 5 cm. in diameter with minimal extension to adjacent structures.
- T<sub>3</sub>—Tumors more than 5 cm. in diameter with limited extension to the adjacent structures.
- T—Massive primary tumor.
- N<sub>0</sub>—No clinical evidence of lymph node metastasis.
- N<sub>1</sub>—Clinically evident single lymph

<sup>\*</sup> Presented at the Sixty-eixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28-October

<sup>1, 1965.</sup>From the Department of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

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node metastasis less than 3 cm. in diameter.

N<sub>2</sub>—Single lymph node metastasis over 3 cm. in diameter, or multiple ipsilateral lymph node metastasis.

N<sub>3</sub>—Large lymph node metastasis with fixation or bilateral metastasis.

DM—Distant metastasis.

From July, 1965 on, 2 and 4 cm. have replaced 3 and 5 cm. to conform with prevailing staging systems.

# CLINICAL FEATURES AND ROUTES OF SPREAD

In addition to the usual exophytic, ulcerative, and infiltrative clinical varieties of spread, there is a diffuse superficial spread. After the first week of treatment these reddish, velvety areas are covered with exudate. This tumoritis delineates the total extent of the disease.<sup>5</sup>

## RETROMOLAR TRIGONE-ANTERIOR FAUCIAL PILLAR (RMT-AFP)

The retromolar trigone is a small strip of mucous membrane, roughly triangular, which covers the ascending ramus starting posterior to the last lower molar and ending at the apex of the tuberosity of the upper maxilla. Because of its location on the ascending ramus, the surgical and radiotherapeutic managements of lesions originating on it are similar to the management of the lesions of the palatine arch.

Unless lesions are very early, both areas are involved (Fig. 1); when more extensive, there are differences in routes of spread which are important in the management. The lesions of the RMT can involve the posterior buccal sulcus, then the masseter muscle, producing trismus, and gain access to the pterygoid space. The medial extensions are into the posterior aspect of the floor of the mouth and the posterolateral border of the tongue, and then anteriorly to the gingiva.

The anterior faucial pillar is formed by the projection of the glossopalatine muscle which arises from the anterior surface of the soft palate and inserts into the side of the



Fig. 1. Typical lesion of retromolar trigone extending anteriorly into buccal mucosa, posteriorly into anterior faucial pillar and inferiorly into gingiva.

tongue. Lesions of the AFP extend anteriorly to the retromolar trigone, posteriorly to the tonsillar fossa and upward and downward along the glossopalatine muscle, *i.e.*, the soft palate and the glossopalatine sulcus into the posterolateral border of the tongue.

#### SOFT PALATE

The soft palate is made of the anterior and posterior faucial pillars which join to form the uvula. Lesions originating on the uvula can extend either along the anterior or posterior faucial pillars or both, but often they extend selectively on the posterior faucial pillars dipping into the posterior aspect of the palatoglossal sulci.

#### TONSILLAR FOSSA

The tonsillar fossa is located between the anterior and posterior faucial pillars. Lesions will extend to both pillars and, pos-

teriorly, into the pharyngeal walls and parapharyngeal space, medially into the glossopalatine sulcus and the base of the tongue.

#### GLOSSOPALATINE SULCUS

The lesions originating in the sulci are not identified as such in the literature. We assign them either to the base of the tongue or the tonsillar areas depending upon which structure is most involved. For early lesions limited to the sulcus or for lesions involving equally the tongue and tonsillar areas, arbitrary decisions have to be made.

#### POSTERIOR FAUCIAL PILLAR

Lesions arise rarely on the posterior faucial pillar. There is early involvement of the lateral and posterior pharyngeal walls, and of the tonsillar fossa.

CORRELATION OF STAGING OF PRIMARY LESION WITH ANATOMIC SITES AND DIFFERENTIATION

Lesions of the tonsillar fossa are staged

T<sub>3</sub> or T<sub>4</sub> (Table 1) more often than those of RMT-AFP or soft palate.

The percentage of Grade I and II lesions diminishes from 69 per cent in retromolar trigone-anterior faucial pillar lesions to 66 per cent in the tonsillar fossa, to 52 per cent on the soft palate. Lymphoepitheliomas are found only in the tonsillar fossa, and are considered Grade IV squamous cell carcinomas

An analysis of the size of the primary lesion (T classification) was done by histologic grading for the individual sites and showed that within anatomic sites the clinical stage is not related to the histologic grade.

#### LYMPH NODE METASTASES

The over-all incidence of lymph node metastases is 58 per cent, 50 per cent for the RMT-AFP, 48 per cent for the soft palate, and 75 per cent for the tonsillar fossa. In relation to clinical staging of primary lesions: 46 per cent of the T<sub>1</sub> and T<sub>2</sub>

Table I

DISTRIBUTION OF LESIONS BY STAGE (TNM) IN 262 PATIENTS TREATED WITH MEGAVOLTAGE IRRADIATION 1954 through December, 1963

(Analysis June, 1965)

Stage		$N_0$	N <sub>1</sub>	N <sub>2</sub>	N <sub>a</sub>
T <sub>1</sub>	RMT-AFP* Tonsillar Fossa Soft Palate	14 4 11	1 2 1		I 2 I
Т.	RMT-AFP Tonsillar Fossa Soft Palate	28 6 6	17 8 1	9 9 2	4 5 2
Т.	RMT-AFP Tonsillar Fossa Soft Palate	19 9 5	6 5 9	14 6 1	5 11 2
T4	RMT-AFP Tonsillar Fossa Soft Palate	4 3 1	1 4	2 5	3 10 2

			Untreated
RMT-AFP	$N_0 = 50\% (65/129)$	$N_0+N_1=70\% (90/129)$	7
Tonsillar Fossa	$N_0 = 25\% (22/89)$	$N_0+N_1=46\% (41/89)$	5
Soft Palate	$N_0 = 52\% (23/44)$	$N_0+N_1=77\% (34/44)$	2

<sup>\*</sup> RMT-AFP = retromolar trigone - anterior faucial pillar.

lesions presented with lymph node involvement compared to 73 per cent of the T<sub>2</sub> and T<sub>4</sub> lesions. Thus, there is a definite correlation between the clinical staging of the primary lesions and lymph node metastases. The incidence of metastases in Grade 11 and 11 lesions was 54 per cent and in Grade 111 and 11 lesions 64 per cent; therefore, the incidence of cervical lymph node metastases is only slightly related to the histologic grading.

An analysis of the initial lymph node distribution (Fig. 2) showed the following:

- 1. The ipsilateral subdigastric lymph node (tonsillar lymph node at the angle of the jaw) is most commonly involved for all three sites, i.e., 57/64 RMT-AFP; 57/67 tonsillar fossa; 17/21 soft palate.
- 2. The submental lymph nodes are rarely involved, 3/152 (2 per cent).
- 3. The ipsilateral posterior cervical triangle involvement shows a considerable variation with the individual sites. The incidence was highest in lesions of the tonsillar fossa (14/67). The incidence is much less in those of the RMT-AFP (4/64) and no posterior cervical metastases were noted in the lesions of the soft palate.
- 4. The incidence of contralateral metastases is highest in the soft palate lesions (8/21), and the same in the tonsillar fossa and the RMT-AFP (13/67 and 11/64, respectively). The primary lesions are close to or reach the midline when there is contralateral neck disease.<sup>12</sup>
- 5. The most commonly involved contralateral lymph node is the subdigastric. This is true for all sites and accounted for 23 of 32 contralateral metastases.
- 6. The retro- and parapharyngeal lymph nodes have been found to be involved in a significant percentage of surgical specimens. At times, the surgeon traced disease to the base of the skull.

# POLICIES OF TREATMENT PRIMARY LESION

The guide lines used for treatment in our institution have been: (1) to design a comprehensive treatment plan for both the primary lesion and the lymphatics of the

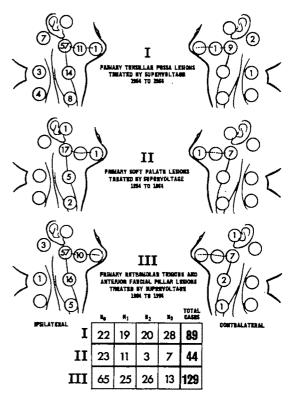


Fig. 2. Frequency and location of cervical lymph node metastases.

- I. Tonsillar fossa: 75 per cent of patients present with metastases. Ipsilateral subdigastric lymph node involvement is most common. Note incidence of posterior chain involvement.
- II. Soft palate: 48 per cent of patients present with metastases. There is frequent contralateral spread but no posterior chain involvement.
- III. Retromolar trigone and anterior faucial pillar: 50 per cent of patients present with metastases. Distribution is similar to tonsillar fossa except for absence of posterior chain involvement. The submental lymph nodes are rarely involved.

neck in a close integration of radiation and surgical procedures, <sup>5, 5, 7</sup> and (2) to accept a percentage of bone complications which can be managed first conservatively, and later, if necessary, by resection of bone.

The exophytic lesions respond better to irradiation probably because they contain a lesser percentage of anoxic cells. Tumor cells in the infiltrative lesions or the infiltrative component of a tumor are poorly oxygenated; primary excision or a combination of irradiation and excision may be indicated in those cases.

With the exceptions of cases of severe

alcoholism or psychologic problems, T<sub>1</sub> and T<sub>2</sub> lesions are treated by irradiation. T<sub>3</sub> and T<sub>4</sub> lesions of the RMT-AFP which have not spread into the pterygoid space are given a tumor dose of 5,000 rads in 5 weeks; a consultation is then held between a head and neck surgeon and a radiotherapist to evaluate the response to treatment. If the lesions are primarily exophytic and the probability of control by irradiation is likely, treatment is carried on to tumor doses of  $6,5\infty$  to  $7,\infty$  rads in  $6\frac{1}{2}$  to 7 weeks. If the lesions are primarily infiltrative, or if there is an infiltrative component in the posterolateral border or the base of the tongue, irradiation may be stopped and a composite operation performed 6 weeks later. In earlier years, supplementary interstitial gamma-ray implants with either radium needles or gold grains were used. Results were unsatisfactory and we now prefer to limit the irradiation to allow a surgical procedure.

#### NECK LYMPH NODES

In general, an elective neck dissection is not done for  $N_0$  cases. Table II shows the policies of management of metastatic neck lymph nodes in an integrated program of radiation and surgical procedures, based on the anaplasticity of the lesion and the staging of the lymph node disease.<sup>10</sup>

The policies shown in Table II are predicated on the capability of moderate doses of radiation to sterilize microscopic disease, to reduce the number of viable cells in an area of gross disease and, therefore, to leave for surgical resection well-localized tumor masses.

To provide maximum skin-sparing, glancing fields or build-up material is not employed. As a rule, modified incisions for the radical neck dissection are used.<sup>11</sup>

#### RADIOTHERAPEUTIC TECHNIQUES

External beam therapy with a Co<sup>60</sup> unit has been the mainstay of treatment. A few patients have been treated with the photon beam of a 22 mev. betatron and more recently with 18 mev. electron beam alone or

half 18 mev. electron beam and half 18 mev. photon beam.

The external beam techniques which may be used are: (1) single homolateral field, (2) parallel opposing fields with equal dosage given to each field, (3) parallel opposing fields loaded in favor of the involved side, (4) paired wedge filtered fields, (5) single homolateral field supplemented with kilovoltage irradiation delivered through an intraoral cone, and (6) external beam therapy supplemented by interstitial implantation with radioactive gold seeds or radium needles. Figures 3 and 4 show, respectively, the common field arrangement and isodose distributions.

#### TABLE II

#### MANAGEMENT OF NECK LYMPH NODE INVOLVEMENT

Retromolar Trigone, Anterior Faucial Pillar, and Soft Palate

- N<sub>0</sub> 5,∞ or 6,∞ rads to ipsilateral neck only through field covering primary lesion; no elective neck dissection
- N<sub>1</sub> 5,∞∞ to 6,∞∞ rads to ipsilateral upper neck through primary field; if involved lymph node is low, 4,∞∞ rads (5∞×8) through separate portal; neck dissection 6 weeks later
- N<sub>2</sub>-N<sub>8</sub> 5,000 to 6,000 rads to bilateral upper neck; 5,000 rads to both lower necks; 6 to 8 weeks later, neck dissection alone or combined with resection of the primary site if indicated by the status of the latter

Tonsillar Fossa

- No 5,000 or 6,000 rads to ipsilateral upper neck
- N₁ 6,000 rads to upper ipsilateral neck and 5,000 to 6,000 rads to contralateral upper neck; 5,000 rads to ipsilateral lower neck; neck dissection only for residual lymph node involvement
- N<sub>1</sub>-N<sub>3</sub> 6,000 rads to upper neck bilaterally; 5,000 rads to lower neck bilaterally; 6 to 8 weekslater, neck dissection alone, or combined with resection of the primary site if indicated by the status of the latter

The weekly dose is 1,000 rads.

When radical neck dissection is not contemplated but cure is attempted, additional radiation to residual neck masses is given. For lesions of the RMT-AFP most of the  $T_1$  and  $T_2$  cases are presently treated with wedge pair filters or one-half electron beam and one-half photon beam to avoid excess irradiation of the opposite side of the pharynx and opposite parotid. The digastric and upper jugular lymph nodes are included in the treatment fields so that a lymph node at the angle of the jaw (tonsillar lymph node) receives the same dose as the primary lesion, usually 6,000 rads in 5 weeks. The para- and retropharyngeal lymph nodes are now included in the treatment fields.  $T_3$  and  $T_4$  lesions are treated with parallel opposing portals to at least 5,000

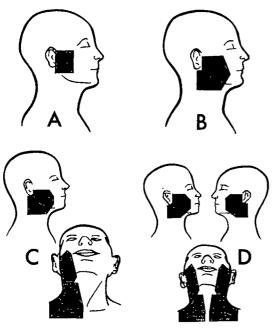


Fig. 3. Field arrangements.

A. Lateral field to include primary lesion only.

B. Inclusion of upper cervical lymphatics in addition to primary lesion with adequate coverage of subdigastric lymph node at angle of mandible.

C. The addition of an anterior field to encompass the lower cervical and supraclavicular area when patients present with lymph node involvement.

D. Parallel opposing fields—equally or differentially loaded to individualized treatment. Arrangement used to treat entire cervical region. Midline shielding is used to spare larynx and trachea. The lateral lobes of the thyroid gland cannot be shielded unless the midjugular lymph nodes are also shielded. Thyroid function must be carefully assessed at follow-up examinations.

rads (1,∞∞ rads per week); if a composite operation is not planned, 1,5∞ to 2,∞∞ rads are given through reduced fields.

For carcinomas of the tonsillar fossa there are 3 basic therapy plans: (1) A pair of oblique wedge filtered portals for a small localized tonsillar fossa cancer—this arrangement includes the primary and homolateral upper neck lymph nodes. (2) Two parallel opposing portals with the 2 to 1 loading favoring the diseased side. If 6,000 rads tumor dose is delivered to the primary lesion, the homolateral lymph nodes will receive approximately 6,500 rads and the contralateral lymph nodes approximately 5,000 rads. When there are large lymph nodes extending posteriorly, the two parallel opposing portals are not of the same size, the contralateral portal being smaller if there are no lymph nodes on that side. The portal on the diseased side covers the spinal cord while the one on the opposite side is aimed only to cover the primary lesion and the jugulo-digastric area. Even if 6,000 rads are given to the homolateral field, the spinal cord will not receive an excessive dose. (3) Two parallel opposing portals with equal loading are used when there is more extensive invasion of the tongue or bilateral neck lymph nodes. The usual dose level is 6,000 rads in 5 weeks. Additional irradiation of 500 to 1,500 rads is given through much reduced portals.

Early lesions of the soft palate which can be encompassed by an intraoral cone may be treated entirely with that modality, delivering 5,500 to 6,000 rads in 4 weeks. For lesions limited to the palate, portals are 7×5 cm. or 6×5 cm. and 6,000 rads are delivered in 5 weeks. A 22 mev. betatron photon beam is preferable when using parallel opposing portals. If a Co<sup>60</sup> unit only is available, it is preferable, whenever feasible, to avoid excessive subcutaneous doses by giving only 5,000 rads with the parallel opposing fields and 1,000 rads through an intraoral cone.

#### ANALYSIS OF CLINICAL MATERIAL

All cases have been recorded on printed

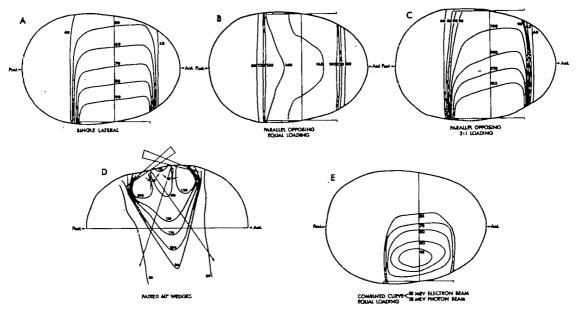


Fig. 4. Isodose distributions.

- A. Single homolateral field.
- B. Parallel opposing fields—equal loading for uniform dose distribution.
- C. Parallel opposing fields—2:1 loading to shift maximum depth dose to side of involvement.
- D. Paired 60 degree wedges.
- E. Combination of 18 mev. photon and electron beams—equal given doses.

code sheets, so that complete summaries of each case are available.

Flow sheets are made with symbols recording the essential information. These flow sheets are useful for quick reference as well as survey of the salient features.

For each anatomic site, an operational chart is made by T and N. The chart for the RMT-AFP is shown as an example (Table III).

Not only survival rates, but also failures, local or in the neck, evolution of lymph node disease, the value of added surgical procedures and complications have been analyzed.

## FAILURES AT THE PRIMARY SITES AND THEIR

All known and unquestionable local failures developed within 19 months (Table IV).

The incidence of failure to control lesions of the RMT-AFP, tonsillar fossa, and soft palate are essentially the same, being re-

spectively 16 per cent, 20 per cent, and 18 per cent.

Of the 21 failures of the RMT-AFP, 8 were in the primary area, 4 in the soft palate, 4 in the tongue and the remainder in the tonsillar fossa, gingiva, glossopharyngeal sulcus, and cheek. Of the 18 primary failures of the tonsillar fossa, 8 were in the tonsillar fossa, 4 in the tongue, and the remainder in the palate, posterior pillar, floor of mouth, pharyngoepiglottic fold, and mandible. Of the 8 failures of the soft palate, 4 were in the palate itself, 2 in the pharyngeal wall and tonsillar fossa and the actual location of 2 is unknown.

In summary, 20 of 47 failures were within the originally involved structure. Failure to control the disease in the tongue occurred only in 8 of 47 lesions. This contrasts with the report of Rider<sup>13</sup> who found that in epithelial lesions of the tonsillar area, failure to control a spread in the tongue is the most common cause of failure.

The management of residual or recurrent

TABLE III RETROMOLAR TRIGONE-ANTERIOR FAUCIAL PILLAR (RMT-AFP) 129 SQUAMOUS CELL CARCINOMAS TREATED WITH MEGAVOLTAGE IRRADIATION 1954 through December, 1963

(Analysis June, 1965)

Stage	N <sub>0</sub>		$N_1$		N <sub>2</sub>		N <sub>3</sub>		Total	
Tı	NED SP P, N	1 I 2 I	NED	I	NED	I	DM	I	NED SP P, N DM	13 2 1
T <sub>2</sub>	NED ID SP Unknown P, N DM Necrosis	14 5 2 2 2 2 2	NED LēD ID SP Unknown P, N DM	6 1 4 1 1 3 1	NED ID SP Unknown Carotid artery P, N	I 2 2 2 2 I I	NED P, N ID	I 2 I	NED LēD ID SP Unknown Necrosis Carotid artery P, N DM	22 1 12 5 5 1
Т,	NED ID SP Unknown P, N DM	8 3 4 2 1	NED ID SP DM	I 2 I 2	NED ID Unknown P, N DM	8 1 2 1 2	ID SP Unknown P, N	I I I 2	NED ID SP Unknown P, N DM	17 7 6 5 4 5
T.	ID Unknown P, N Suicide	I I I	SP	I	P, N Necrosis	I	ID P, N DM	I	Necrosis ID SP Unknown P, N DM Suicide	1 2 1 1 3 1
Total	NED ID SP Unknown P, N DM Necrosis Suicide	33 9 8 5 5 3 1	NED LēD ID SP Unknown P, N DM	8 1 6 3 1 3 3	NED ID SP Unknown Carotid artery P, N DM Necrosis	10 3 2 4 1 3 2 1	NED ID SP Unknown P, N DM	I 3 I I 5 2	NED LēD ID SP Unknown P, N DM	52 1 21 14 11 16 10

Key: NED = no evidence of disease.

SP = subsequent primary lesions.

P,N = primary and neck disease.

ID = intercurrent disease.

DM = distant metastases.

LcD = lives with disease.

TABLE IV

TIME OF APPEARANCE OF RECURRENCES\*
1954 through December, 1963

(Analysis June, 1965)

Months	Number
o- 3	12†
o- 3 4- 6	10
7- 9	8
10-12	8 38 within 12 months
13-18	4
19	1 43 within 19 months
58 60	ı
60	I 45

<sup>\*</sup>Two at unknown time.

The late recurrences, at 58 and 60 months, were in patients with tonsillar fossa lesions T<sub>2</sub> and T<sub>4</sub>, respectively. Both recurrences were in the tongue. Although these recurrences could represent new primary lesions, they are scored as late recurrences since they are within the irradiated field.

disease has always been by surgical resection because re-irradiation would almost always result in a combination of active disease and necrosis. Table v shows the incidence of primary recurrence and the results of surgical resection according to

anatomic sites and extent of the primary lesion. The results of treating a recurrence by surgical resection are most gratifying in lesions of the RMT-AFP.

#### DISEASE IN THE NECK

Table vI shows the NED (no evidence of disease) rate at 2 years by lymph node staging. The numbers are too small for statistical significance; only trends are indicated.

Survival rates for N<sub>2</sub> patients are consistently better than for N<sub>1</sub> patients. A previous analysis had shown close percentages. These results are not readily explainable as one would expect, similar to those previously found for the oral cavity, a significant drop in survival rates between the N<sub>1</sub> and N<sub>2</sub> patients.

A possible explanation is the increasingly systematic use of whole neck irradiation in the N<sub>2</sub> cases.<sup>6,10</sup> The worthwhile results in the N<sub>8</sub> cases are also strongly suggestive of the value of radiation to the whole neck prior to radical neck dissection or its use alone.

Between 1954 and 1964, 80 patients have had a radical neck dissection (Table VII).

Table V

RECURRENCES BY STAGES IN PATIENTS TREATED WITH PRIMARY MEGAVOLTAGE IRRADIATION
AND THEIR SURGICAL MANAGEMENT
1954 through December, 1963

(Analysis June, 1965)

Site	Stage	Number	Recurrences	Treatment by Surgery	No Local Evidence of Disease
RMT-AFP	T <sub>1</sub> T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	17 58 44 10 (129)	2 10 7 2 (21)	2 5 — (12)	1/2 4/5 5/5 — (10/12)
Tonsillar Fossa	T <sub>1</sub> T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	8 28 31 22 (89)	3 5 9 (18)	1 - 2 1 (4)	1/1 — 1/2 1/1 (3/4)
Soft Palate	T <sub>1</sub> T <sub>2</sub> T <sub>3</sub> T <sub>4</sub>	13 11 17 3 (44)	2 3 3 (8)		

<sup>†</sup> Four clinical persistence.

Table VI
TONSILLAR REGION SURVIVAL (NED\*) BY N STAGE AT 24 MONTHS
1954 through December, 1963‡

(Ana	lysis	June,	1965)

Site	N <sub>0</sub>	$N_1$	N <sub>2</sub>	N <sub>3</sub>	Total
RMT-AFP Tonsillar Fossa Soft Palate	$48/65\dagger = 74.0\%$ 12/22 = 55.0% 18/23 = 78.0%	9/19=47.0%	16/26=61.5% 11/20=55.0% 2/3 =66.0%	11/28 = 39.0%	

<sup>\*</sup> NED = no evidence of disease.

Of these 80 patients, 49 had received previous neck irradiation. In 42 of the 49 patients, at least one side of the neck was included in the treatment fields because of advanced neck disease. In the remaining 7 patients, all with lesions of the RMT-AFP, the volume was limited to only the upper ipsilateral neck. Thirty-six of the patients received at least 5,000 rads given dose to the entire cervical region. The patients without preoperative irradiation were initially  $N_0$ .

The over-all incidence of failures after radical neck dissection is 14 per cent (11 of 80). Eight of these neck failures occurred after previous irradiation (16 per cent).

This percentage is comparable to a 13 per cent recurrence at 1 year in a series of patients, the majority with oral cavity primaries, who had a radical neck dissection at Memorial Hospital after a preoperative radiation dose of 2,000 rads in 5 days, contrasting with a 33 per cent local recurrence at 1 year in a control group determined by randomization without preoperative irradiation.<sup>9</sup>

Histologic findings in the surgical specimens showed positive lymph nodes in 22 out of 31 cases without previous irradiation (71 per cent) and 28 in 49 patients with previous irradiation (56 per cent).

The incidence of complications for neck

Table VII

RECURRENCES IN THE NECK IN PATIENTS WITH RADICAL NECK DISSECTION
1954 through December, 1963

(Analysis June, 1965)

Site	Total No.	After	No Previous	Total*	Complications after Preoperative Irradiation		
Site	of Patients	Irradiation	Irradiation	1 otal	Moderate	Carotid Artery Rupture	
RMT-AFP Tonsillar Fossa Soft Palate	129 89 44	3/25† 3/16 2/8	3/21 0/6 0/4	6/46 3/22 2/12	5 7 3	2 I O	
Total	262	8/49 (16%)	3/31 (10%)	11/80	15	3‡	

<sup>\*</sup> Including composite operations.

<sup>†</sup> Ratio=NED at 24 months
Total

I Some patients with only 18 month follow-up.

<sup>†</sup> Seven with limited volume irradiation in RMT-AFP.

<sup>‡</sup> Two died, 1 alive.

dissection after irradiation was 36 per cent (18/49). Fifteen of these complications were considered mild to moderate, *i.e.*, delayed healing, necrosis of skin flap, post-operative edema, and fistula formation. In 3 cases, however, the complication was carotid artery rupture. One of the 3 patients is still alive.

#### EVOLUTION OF LYMPH NODE DISEASE

An analysis of the evolution of lymph node disease has been made. Initially, 65 patients with lesions of the RMT-AFP were No and only 4 ever developed lymph node disease. Twenty-two of the patients with tonsillar fossa lesions were initially N<sub>0</sub> and none of these patients developed cervical metastasis. Twenty-three of the patients with soft palate lesions were initially N<sub>0</sub> and only 1 has developed cervical lymph node metastases. Duffy<sup>8</sup> found that 12 per cent of patients with squamous cell carcinomas of the tonsillar area, initially without lymph node metastasis (N<sub>0</sub>), developed lymph node metastasis later and for patients with soft palate lesions, the incidence was 17.7 per cent. These data suggest the value of elective irradiation as previously reported.12

#### SURVIVAL RATES AND SITES OF FAILURE

Table VIII shows the absolute and de-

terminate survival rates for the patients treated.

There is a sharper drop in survivors between 3 and 5 years than, for instance, in patients with cancer of the cervix where the difference between 3 and 5 year survival rates is less than 10 per cent. Intercurrent diseases, because of old age and development of other primary lesions, are responsible for deaths.

The sites of failure and causes of death at any time of the follow-up are tabulated in Table IX. The good control of the disease obtained at the primary site and in the neck contrasts with experience of the past,<sup>4</sup> when 80 per cent of deaths were due to failure of controlling disease above the clavicle.

#### COMPLICATIONS OF RADIOTHERAPY

An analysis of the complications has been done in great detail for the tonsillar area for 176 patients treated from 1954 through 1962.8

Soft tissue necrosis is uncommon. Bone exposure of the mandible is a complication arising following heavy irradiation of the mandible when the overlying mucous membrane is interrupted either by trauma, local necrosis, or dental surgery. Healing is slow and infection may enter the mandible and, because of damage to small vessels,

Table VIII

SURVIVAL RATES FOR PATIENTS TREATED WITH MEGAVOLTAGE IRRADIATION
1954 through December, 1963

(Analysis June, 1965)

	RMT-AF	P Per Cent	Tonsillar Fossa	Per Cent	Soft Palate	Per Cent
3 yr. Absolute* 3 yr. Determinate† 5 yr. Absolute‡ 5 yr. Determinate†	49/91 49/73 19/52 19/36	53.8 67.1 36.5 53.0	29/66 29/58 19/52 19/42	43.9 50.0 36.5 45.2	22/34 22/31 9/18 9/15	64.7 71.0 50.0 60.0
	Untreated	RMT-AFP	Tonsillar Fo	ossa Soft I	Palate	
	* 3 yr. ‡ 5 yr.	3 2	2 2	2		

<sup>†</sup> Patients having died from intercurrent disease or subsequent primary lesion and patients with no evidence of disease from the original primary lesion are excluded. No patient has been completely lost to follow-up; whenever there was doubt as to the status prior to death, the patients have been counted as dead from the original disease.

#### TABLE IX

# SITES OF FAILURES AND CAUSES OF DEATH WITH UNLIMITED FOLLOW-UP IN PATIENTS TREATED WITH MEGAVOLTAGE IRRADIATION 1954 through December, 1963

#### (Analysis June, 1965)

	Total	Total		Disease Uncontrolled above Clavicle				0	ther	Causes			
Site	No. of Patients	No. of	Р	N	P, N	Total	DM	ID	Necro-	SP	Un- known	Post- operative Compli- cations	Total
RMT-AFP Tonsillar	129	76	5	5	7	17	IO	24	2	12	10	I	59
Fossa Soft	89	55	6	8	9	23	8	10	_	5	9		32
Palate	44	24	4	5	4	13	_	3	_	4	4	-	II

P=primary uncontrolled.

N=neck disease uncontrolled.

P,N=primary and neck disease uncontrolled.

DM=distant metastases.

ID=intercurrent disease.

SP=subsequent primary lesions.

chronic osteitis may develop.

Fifty-seven of the 69 bone exposures occurred within the first year of the follow-up period, 41 within the first 6 months; 7 developed during the second year; 4 during the third year treatment; and a single incidence was observed 71 months following irradiation of the primary lesion. In 14 of the 19 patients who required hemimandibulectomy, the onset of osteonecrosis was noted within the first 9 months of follow-up.

Many of the bone exposures were of a mild temporary nature. Twelve of the 69 persisted I month or less and a total of 50 persisted less than I year. Fifty-three of the 69 (76.8 per cent) healed on conservative therapy. Pain may be severe when the bone is exposed. Bone exposure is first treated by application of zinc peroxide packing in carboxymethyl cellulose. If healing does not occur, a segmental resection of the mandible or hemimandibulectomy is often necessary for relief of pain and not because of osteitis.

Although many factors may contribute to the development of the bone exposure, 2

of the most obvious ones are the volume of tissue irradiated and the total dose received. The dose of interest is that delivered to the mandible rather than the points in or medial to the tumor. There is a correlation between the stage of the disease and the incidence and severity of complications (Table x). Table x18 gives the incidence of bone exposures and osteonecroses according to the 6 most common radiotherapeutic techniques. The incidence of bone exposure for the equally loaded parallel opposing fields and a single homolateral field, respectively, is 13 and 48 per cent. The incidence of bone necrosis requiring mandibulectomy fairly well parallels that of bone exposure. With wedge filters there is a 45 per cent incidence of bone exposure as well as the significant rate of bone resections. It appears that equally loaded parallel opposing fields give the lowest incidence of bone exposure and osteonecrosis. The use of this technique, however, gives rise to other complications.

Prophylactic dental care must be carried out prior to radiation therapy.

Other complications<sup>8</sup> encountered were

TABLE X

BONE EXPOSURES AND JAW RESECTIONS ACCORDING TO STAGE OF PRIMARY LESION IN 176 PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE TONSILLAR AREA 1954 through December, 1962

(Analysis October, 1964)

Stage	No. of Pa- tients		Severe Necroses Requiring Man- dibulectomy
$T_1+T_2$ $T_3+T_4$	88	29.5%	6.8%
	88	45·4%	14.8%

dryness of the mouth, residual edema, trismus, hearing loss, facial edema, and carotid artery rupture. The true incidence of these complications, particularly that of dryness, is difficult to evaluate. Certainly it is believed that some degree of dryness is experienced by almost every patient treated for a tonsillar area lesion. Dryness was more common in patients treated with parallel opposing fields and less common when more localized therapy was used.

Residual edema is an infrequent complication seen only in patients who have extensive lesions. Trismus is more common in patients treated with a single homolateral field since the masseter muscle on the involved side, like the mandible, is heavily irradiated.

#### MULTIPLE PRIMARY LESIONS

The incidence of subsequent primary lesions developing in the respiratory and digestive tract including the esophagus is 8.7 per cent for the RMT-AFP, 8.5 per cent for the soft palate, and 10 per cent for the tonsillar fossa lesions.<sup>2</sup> These primary lesions can develop anywhere; approximately 40 per cent were in the hypopharynx, esophagus, and lung. The majority of the patients were above 60 years of age.

Five of 26 patients with primary RMT-AFP lesions also presented with simultaneous lesions. An additional 13 had second lesions within 3 years of their initial lesion or a total of 18 out of 26 within the first 3 years. In the soft palate, 6 of 12 patients presented with simultaneous lesions. An additional 3 were noted within the 3 years of the treatment of the primary lesion for a total of 9 out of 12 cases within 3 years of the diagnosis of the first primary lesion. In the tonsillar fossa, 4 of 22 patients presented with simultaneous lesions. An additional II had a second lesion within the first 3 years of observation for a total of 15 out of 22 within 36 months of treatment of primary lesions.

An analysis of the effect on survival of the second primary lesion is very difficult. It is obvious that the effects depend mainly on the location of the second primary le-

TABLE XI

INCIDENCE OF BONE EXPOSURE AND OSTEONECROSIS BY TECHNIQUES IN 176 PATIENTS
WITH SQUAMOUS CELL CARCINOMA OF THE TONSILLAR AREA

1954 through December, 1962

(Analysis October, 1964)

Techniques	No. of Patients	Per Cent of Patients with Bone Exposure	Per Cent of Patients with Necroses Requiring Mandibulectomy
Single homolateral field Unequally loaded parallel opposing fields	50 64	24 (48.0%) 22 (34.4%)	9 (18.0%) 4 ( 6.25%)
Equally loaded parallel opposing fields	14	2 (34.4%)	0.2570)
Paired wedge filter fields	22	10 (45.5%)	3 (13.6%)
External irradiation plus interstitial implanta- tion of radioactive sources	12	4 (33.3%)	2 (16.7%)
Single homolateral field plus intraoral cone	14	4 (28.6%)	1 (7.1%)

sion. Patients presenting with hypopharyngeal, lung, and esophageal lesions have a very bleak outlook compared to those presenting with lesions within the oral cavity. Second lesions within the upper respiratory tract have a fair prognosis.

#### CONCLUSIONS

Progress has been made in the last 2 decades in the management of the lesions of the tonsillar area and palatine arch. This is manifested by increased survival rates and also by increased freedom from local disease or disease in the neck.

The management of the primary lesion is essentially radiotherapeutic with a surgical resection kept in mind for specific indications.

The primary surgical resection of diffuse neck disease or disease which has spread beyond the capsule of the lymph nodes is fraught with a high incidence of local recurrences and the increased freedom from disease in the neck can be attributed to the very close combination of radiation therapy and surgery.

Adjustment in radiotherapeutic and surgical techniques have evolved through the years to minimize complications.

Gilbert H. Fletcher, M.D.
Department of Radiotherapy
The University of Texas
M. D. Anderson Hospital and Tumor Institute
Houston, Texas

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# END RESULTS OF RADIOTHERAPY IN LARYNGEAL CANCER BASED UPON CLINICAL STAGING BY THE T.N.M. SYSTEM\*

By RALPH M. CAULK, M.D. WASHINGTON, D. C.

THE author was privileged to serve on the initial Task Force Committee which submitted the clinical stage classification for carcinoma of the larynx that was later approved by the American Joint Committee on Cancer Staging and End Result Reporting.<sup>1</sup> It was surprisingly easy to personally review all of the material and stage it by the T.N.M. system with what is more than likely a high degree of accuracy. The survival rates have been calculated by the actuarial or life method as outlined by the American Joint Committee brochure<sup>2</sup> on Reporting of Cancer Survival and End Results. The actuarial or life table method utilizes all survival information accumulated up to the closing date of the study and describes the manner in which the patient group was depleted and the total period of observation. It also enables one to utilize data on those patients who died in the interval free of disease and those who were lost to follow up. When a survival curve such as this is compared with a so-called expected survival rate,3 many of the inconsistencies inherent in other methods of survival rate reporting are eliminated.

The material has been divided into the 3 anatomic regions of the larynx; viz., glottic, supraglottic, and subglottic and the T.N.M. designations applying to these regions and divisions thereof.

No attempt was made to assess the overall survival of this material because almost from the very beginning when we began to accumulate cases for treatment it became apparent that a high degree of selection was necessary if we were justified in treating laryngeal cancer by irradiation at all. As a consequence, the early initial philosophy was that radiation therapy probably had little to offer from the standpoint of cure of advanced laryngeal cancer and, therefore, with everything else being equal, we should limit treatment to only the early cases in which there is a good prospect for long term survival. The judgment in this respect has been well borne out by other authors and by the material herein presented.

The material on which this paper is based represents 202 cases of cancer originating in the larynx treated between the years 1933 through 1964 at the Department of Radiology at the Garfield Hospital and the Washington Hospital Center. There are only 2 cases lost to follow-up. The facilities of the Garfield Memorial Hospital merged with those of the Washington Hospital Center in March, 1958. Some of the material has been utilized in a different fashion in previous publications.4-6 This study embraces only those cases in which roentgen therapy was the initial definitive form of treatment. The homogeneity of the sample is demonstrated in Table 1 in which the relationship of age, sex, race and private-staff patient ratio is shown. These data are recorded in 5 year increments and leave no doubt that these factors are sufficiently consistent to render the statistical information valid. For the purpose of plotting a normal expected survival curve, life expectancy of 60 year old males was used.

The material is also homogeneous with respect to the philosophy of the treatment which was employed during this period of time. The author was associated in the Department from 1935 through 1942 and

From the Department of Radiology, Washington Hospital Center, and Radiologic partnership of Drs. Groover, Christie and Merritt.

<sup>\*</sup> Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October 1, 1955.

Table I

BASIC COMPOSITION OF THE SAMPLE

	Average Age (yr.)	Male	Female	White	Negro	Private	Stafi
1933-1939	59.6	16	2	16	2	14	4
1940-1944	56.7	15	4	17	2	17	2
1945-1949	60.8	19	I	18	2	12	8
1950-1954	61.6	20	2	18	4	15	7
1955-1959	61.1	<b>4</b> 7	4	48	3	45	6
1960-1964	61.2	66	6	65	7	59	13

from 1946 to date. The general philosophy relative to total dose, fractionation and total treatment time throughout the entire period closely approximates criteria acceptable as of this date. It was not until 1958 that supervoltage apparatus became available; prior to that all treatment was given in the orthovoltage range.

Tables II, III and IV present the survival data in detail based upon the anatomic region in which the cancer originated. The data are further presented by stages and T.N.M. designations. It did not seem desirable to list the details of survival in those stages in which there were no long-term survivals and were obvious failures to cure. These survival data include those cases which were radiation failures and subjected to surgery at a later date. This matter will be further discussed below.

It might be worthwhile to speculate on

the rather promising results evidenced in the few cases of cancer of subglottic origin. Martin<sup>5</sup> firmly believed that all subglottic cancer is essentially a downward extension of cancer of the vocal cords. The late Chevalier Jackson in a personal communication was contrary minded and believed that true subglottic cancer did exist. The cases herein recorded would certainly fulfill the criteria for subglottic cancer in that the disease involved the vocal cord or cords and extended downward into the subglottic region and into the trachea. The author is personally of the opinion that these cancers may well have been cancers of the trachea which extended upward to involve the cords. The radiosensitivity and curability are consistent with his experience in tracheal cancers not associated with the larynx in material yet to be reported.

Table v presents the detailed composite

TABLE II

LARYNGEAL CANCER OF GLOTTIC ORIGIN—SURVIVAL DATA

Standard (expected) Survival	No. of Cases	1 Yr. %	2 Yr. %	3 Yr. %	4 Yr. %	5 Yr. %
	•	97.8	95.4	92.8	90.1	87.3
Stage I						
$T_1N_0M_0$	98	99	90	83	80	80
Stage II		,,,		Ü		
$T_2N_0M_0$	27	96	88	84	79	66
$T_3N_0M_0$	7	85	17	17	17	17
$T_4N_0M_0$	2	-	•	(failure to cure		,
Stage III				•		
$T_2N_1M_0$	I			(failure to cure	)	
$T_3N_1M_0$	I			(failure to cure		

TABLE III

LARYNGEAL CANCER OF SUPRAGLOTTIC ORIGIN—SURVIVAL DATA

Standard (expected) Survival	No. of Cases_	1 Yr. %	2 Yr. %	3 Yr. %	4 Yr. %	5 Yr. %
		97.8	95-4	92.8	90.1	87.3
Stage I						
$T_1N_0M_0$	11	91	82	73	64	64
Stage II		-		.0	•	•
$T_2N_0M_0$	14	93	86	64	49	40
$T_2N_0M_0$	10	80	71	47	47	47
$T_4N_0M_0$	12	Ιయ	50	20	20	20
Stage III			3			
$T_3N_1M_0$	2		1	(failure to cure	e)	
$T_4N_1M_0$	2			failure to cure		
Stage IV				-	-	
$T_2N_2M_0$	4		1	(failure to cure	:)	
$T_3N_2M_0$	İ			failure to cure		
$T_4N_2M_0$	3			failure to cure		

data of all the cases regardless of the anatomic site of origin by their respective stages and T.N.M. designations.

The identical material is presented in graph form in Figures 1, 2 and 3. Due to the small number of cases of subglottic cancer, they are not presented in this fashion.

#### POSTRADIATION SURGERY

There are 28 cases in this entire group which underwent subsequent surgery for uncontrolled disease.

On I case a successful hemilaryngectomy was done for what was believed to be a new cancer developing  $7\frac{1}{2}$  years after the initial treatment. The remaining cases can be categorized as true failures to cure by means of the initial roentgen therapy.

GLOTTIS, STAGE I, T1N0M0-II CASES

One has undergone successful salvage by means of a laryngofissure, 3 have been successfully salvaged by means of a hemilaryngectomy and 4 have been successfully treated by means of a total laryngectomy. In 3 cases the surgery, consisting of a total laryngectomy, has not resulted in cure.

One can speculate on the failures for cure in this group of early and relatively early glottic lesions and, in reviewing the material, it would seem that at least 4 of the failures were due to an inadequate total dose. In 2 additional cases the disease, while classified as Stage I, was believed to be more advanced than that at the time of treatment. In the remaining cases, there is no obvious reason for radiation failure.

Table IV

LARYNGEAL CANCER OF SUBGLOTTIC ORIGIN—SURVIVAL DATA

Standard (expected) Survival	No. of Cases	1 Yr. %	2 Yr. %	3 Yr. %	4 Yr. % 90.1	5 Yr. % 87.3
		97.8	95.4	92.8		
Stage I						
$T_1N_0M_0$	2	100	100	100	100	100
Stage II						
$T_{\bullet}N_{0}M_{0}$	2	100	100	100	100	100
$T_4N_0M_0$	r	100	100	100	100	100

Table V

LARYNGEAL CANCER—SURVIVAL DATA BY STAGES REGARDLESS OF ANATOMIC REGION

Standard (expected) Survival	No. of Cases	1 Yr. %	2 Yr. %	3 Yr. %	4 Yr. %	5 Yr. %
		97.8	95 · 4	92.8	90.1	87.3
Stage I						77000000
$T_1N_0M_0$	110	96.6	90.6	85.3	81.3	81.3
Stage II			-			ŭ
$T_1N_cM_0$	4 I	94.5	87.0	74.0	64.0	53.0
$T_3N_0M_0$	19	88.3	62.6	54.6	54.6	54.6
$T_4N_0M_0$	15	66.0	50.0	40.0	40.0	40.0
Stage III						
$T_2N_1M_0$	I			(failure to cure	:)	
$T_3N_1M_0$	5			(failure to cure	<del>:</del> )	
$T_4N_1M_0$	3			(failure to cure	:)	
Stage IV						
$T_2N_0M_0$	4			(failure to cure	·)	
$T_3N_0M_0$	I			(failure to cure		
$T_4N_0M_0$	3			(failure to cure	·)	

#### GLOTTIS, STAGE II, TaNoMo

There were 5 cases in this category in which radiation failed to cure, and 3 of these have undergone successful post-irradiation total laryngectomies, and I has undergone successful hemilaryngectomy.

#### SUPRAGLOTTIS, STAGE I

There is only I radiation failure in this group of patients who were subjected to subsequent surgery, a total laryngectomy, and this has been a successful venture.

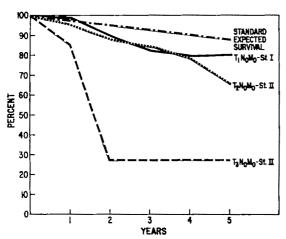


Fig. 1. Survival curve of patients with laryngeal cancer of glottic origin.

#### SUPRAGLOTTIS, STAGE II, T2N0M0

There are 3 cases in this category, 2 of which underwent a total laryngectomy with a good result, and another a partial laryngectomy with a good result.

#### SUPRAGLOTTIS, STAGE II, $T_8N_0M_0$

There are 3 radiation failures in this category, 2 of which were subjected to a total laryngectomy with a poor result, and in I case an excellent result was obtained.

#### SUPRAGLOTTIS, STAGE II, T4N0M0

There are 3 cases in this category all

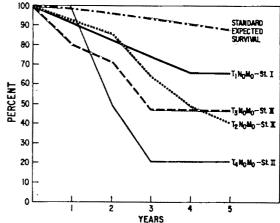


Fig. 2. Survival curve of patients with laryngeal cancer of supraglottic origin.

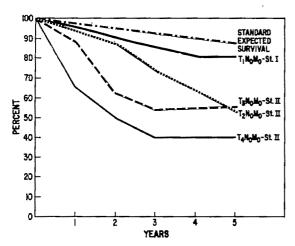


Fig. 3. Survival curve of patients with laryngeal cancer of all anatomic regions.

subjected to total laryngectomy, none of which was cured.

#### SUPRAGLOTTIS, STAGE IV, T4N1M0

There was I patient in this category who was submitted to a total laryngectomy with failure to cure.

#### COMMENT

It is not the purpose of the author to go into detail as to the problems concerned with surgical treatment of radiation failures in laryngeal cancer. The experience with these 28 cases, however, has indicated that the various procedures can be accomplished with surprisingly few complications and many of these are not entirely attributable to the previous radiation therapy. It is probable that postirradiation surgery is most successful when it is done in those cases in which the field of radiation therapy has been quite small and the lines of surgical excision are beyond the tissue subjected to ionizing radiation.

#### SUMMARY

The value of the T.N.M. system of staging laryngeal cancer that has been approved and recommended by the American

Joint Committee on Cancer Staging and End Result Reporting has been shown. The survival rates calculated by the actuarial or life method also recommended by the American Joint Committee have been utilized. It is recognized that, while the material presented demonstrates to a degree the efficacy of roentgen therapy in the management of early laryngeal cancer, it does not completely demonstrate the inefficacy of radiotherapy in some of the more advanced lesions. This is by virtue of the fact that there are insufficient cases in these categories to render the statistics entirely valid. This study has also shown that surgery can be very useful in the management of certain cases of radiation failure.

Department of Radiology Washington Hospital Center 110 Irving St., N. W. Washington, D. C. 20010

The author wishes to thank Mr. Fred Ederer, Biostatistician to the National Institutes of Health, Bethesda, Md., for his helpful advice in the preparation of the statistical data.

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## AN UNUSUALLY HIGH NASAL UPTAKE OF RADIOACTIVE IODINE DURING TREATMENT FOR CARCINOMA OF THE THYROID\*

By V. R. McCREADY, M.Sc., M.B., B.Ch., D.R.M.D. sutton, surrey, england

THE advent of radioisotope scanning has greatly facilitated the detection of secondary carcinoma of the thyroid. However, physiologic concentration of the radioactive iodine may cause confusion in the interpretation of the scans. It is well known, for example, that radioactive iodine is excreted in the saliva<sup>7</sup> and by the stomach<sup>6</sup> and in the latter case there is sufficient concentration even to permit diagnostic scans.2 Accumulation of radioactive iodine may also be seen on scanning the liver and bladder.8 Secretion of iodine in the milk was noted in 1938 by Elmer<sup>8</sup> and more recently the possibility of uptake in the breast being confused with secondary thyroid carcinoma has been pointed out by Zalis et al.10 The following case illustrates an example of an unusually high nasal concentration of radioactive iodine posing a diagnostic problem during the treatment of a carcinoma of the thyroid.

#### REPORT OF A CASE

The patient, a female aged 65, was first seen complaining of dyspnea of gradual onset over a period of 15 months. Her only other complaint was a loss of 14 pounds of weight during the previous year. The past medical history revealed nothing relevant except that 15 months previously there had been one bout of epistaxis.

On examination there was stridor and dyspnea. Palpation of the neck revealed diffuse infiltration of the right lobe of the thyroid gland, while there was a small hard well circumscribed nodule at the lower pole of the left lobe. The chest roentgenogram was normal. Tracheoscopy was performed and the trachea was found to be narrowed about I inch from the vocal cords by what seemed to be invasion by a tumor. A specimen was taken for biopsy from the right lobe

and histology showed papillary adenocarcinoma.

The diagnosis of carcinoma of the thyroid having been made, an ablative dose of 80 mc of I<sup>131</sup> was given orally. Six weeks later a therapy dose of 150 mc was given since a neck scan at that time had shown concentration of iodine mainly on the right side over the enlargement, while the uptake on the left was minimal. A longitudinal profile scan 4 days after the therapy dose showed iodine uptake over the face in the region of the nose and mouth (Fig. 2A). Careful scanning of this area showed discrete radioactive iodine uptake on the right side and slightly posterior to the tip of the nose (Fig. 1, A and B). The scan was repeated with the same result after thorough cleansing of the nose with saline. The effective half life of the nasal activity was 48 hours while that of the neck activity was 35 hours, confirming that the nose had not been accidentally contaminated.

Two weeks after the first therapy dose, she experienced another episode of epistaxis which ceased without medical treatment. Four weeks later the neck tumor on the right side was found to have regressed clinically, while a possible slight increase was noted in the size of the nodule on the left. A tracer dose of 500  $\mu$ c of I<sup>181</sup> was given orally and a scan confirmed the presence of a decreased area of uptake on the right side. Following a profile scan (Fig. 2B), counting over the nose revealed an uptake of 3 per cent at 2 hours decreasing to 1.5 per cent at 24 hours. A swab from the inside of the nose at 24 hours contained only 0.3 µc I<sup>181</sup>. Second and third therapy doses continued to produce tumor regression on the right side of the neck while the mass on the left side, which had never taken up iodine, appeared to increase slightly in size. Whole body profiles and scans of the nose continued to show uptake of the radioactive iodine until more activity was present in the nose than in the neck (Fig. 2, C and D).

<sup>\*</sup> From the Radiotherapy Research Unit, Institute of Cancer Research: Royal Cancer Hospital, The Royal Marsden Hospital, Downs Road, Sutton, Surrey, England.

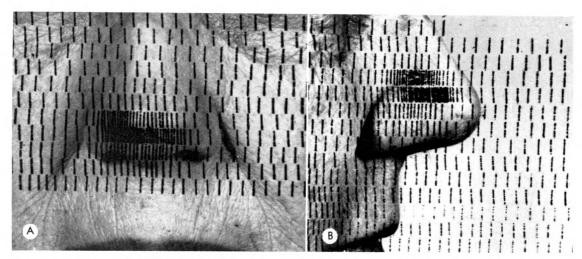


Fig. 1. (A) Anterior scan of the nasal region. (B) Lateral scan of the same region.

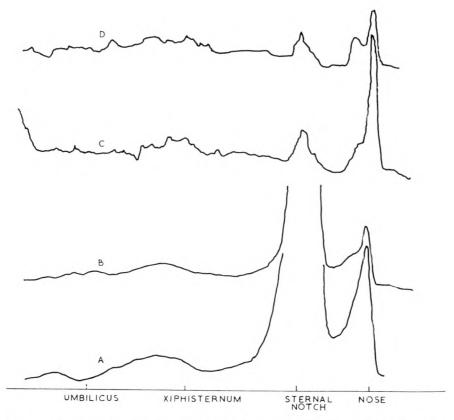


Fig. 2. Profile scans of the patient. (A) Four days after the first therapy dose. (B) Six days after 500 microcuries  $I^{131}$  prior to the second therapy dose. (C) Three days after the second therapy dose. (D) Three days after the third therapy dose.

#### DISCUSSION

Radioactive iodine has been found in nasal secretions on scanning after a 5 mc dose of radioactive iodine was given to a thyroidectomized patient<sup>9</sup>. In this case, however, in view of the relatively high nasal activity and the history of epistaxis, the possibility of a secondary carcinoma had to be considered although carcinoma secondary to a papillary adenocarcinoma of the thyroid is generally found first in the cervical lymph nodes.<sup>1</sup> Aberrant thyroid tissue was considered but it was thought to be unlikely and in any case it would have ceased to function after the ablative dose of radioactive iodine.

After the detection of radioactivity on the nasal swab, it was felt that the concentration of radioactive iodine must have been physiologic. The virtual absence of nasal secretions, the low activity on the swab and the high nasal activity suggest that it was located mainly in the tissues.

This high concentration of radioactivity in the vestibule is, nevertheless, still puzzling since, although active secretion by the salivary, gastric, and mammary glands is well documented,<sup>4-7</sup> there is no similar glandular epithelium in this region. Glands are present elsewhere in the nasal cavities, but it would appear that, at least in this case, they did not secrete the radioactive iodine.

It is hoped that this case report will help avoid another diagnostic pitfall in radioisotope scanning in cases of secondary carcinoma of the thyroid.

Isotope Unit Royal Marsden Hospital Downs Road Sutton, Surrey, England My thanks are due to Professor D. W. Smithers for permission to publish this case history. I am grateful to Dr. E. O. Field for his help and encouragement, and to Mrs. E. Gillian for technical assistance.

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## ROENTGENOGRAPHIC DIAGNOSIS OF THYROID CANCER IN THE PRESENCE OF ENDEMIC GOITER

By SERVIO TULIO ERAZO, M.D.,\* and HEINZ W. WAHNER, M.D.†

THE differential diagnosis between thyroid cancer and goiter in the presence of a nodular thyroid gland presents challenging problems to the diagnostician. This is particularly true in an endemic goiter area where a high percentage of the population has thyroid tumors and the surgical removal of a great number of them is not feasible because of inadequate local medical facilities. An enlarged thyroid gland is not necessarily the primary site of malignancy in patients who are seen with metastatic carcinoma. Anatomic relations of the organs in the neck are often difficult to evaluate by clinical means alone in patients with large goiters. However, an accurate assessment of these relationships is necessary to plan adequate surgical intervention. For this reason, we have studied soft tissue roentgenography of the thyroid gland in patients with thyroid carcinoma and goiter in an attempt to learn the value of roentgenography in the differential diagnosis of these two diseases.

Attempts at the roentgenographic diagnosis of carcinoma of the thyroid gland have been made in the past. The diagnostic value of tracheal deviation was first studied by Ritvo.7 Other techniques which have been proposed have not been widely accepted because they are too complicated. Among these techniques, pneumoradiography<sup>6,8</sup> is of limited value in case of capsular infiltration. Thyroid arteriography<sup>1-4</sup> may be a useful procedure, but unfortunately requires special skill and equipment in order to yield useful information. Tomography has been used to demonstrate invasion of the trachea, as well as paralysis of the vocal cords. Characteristic calcifications

due to formation of psammoma bodies in malignant tumors have been described as diagnostic signs by Holtz and Powers.<sup>5</sup>

#### METHOD

Clinical records, pathology reports and roentgenograms of 115 patients who had thyroidectomy for nodular or diffuse euthyroid goiter during the period between 1959 and 1964 at the University Hospital in Cali, were reviewed. Twenty-eight had satisfactory roentgenograms of the neck and chest. There were 22 females and 6 males. Their age ranged from 19 to 62 years. These patients had a history of goiter of from 6 to 47 years in duration, with an average of 18 years. There were 21 cases with nodular parenchymatous goiter, 5 with colloid goiter and 2 cases with bacterial thyroiditis.

A group of 105 patients with thyroid cancer seen at the University Hospital during the same period of time comprised the second part of this study. In 47 cases a complete roentgenographic examination of the neck in two planes, a barium study of the esophagus and a chest roentgenogram were available for study. There were 34 females and 13 males, ranging in age from 22 to 69 years. The histologic diagnosis was anaplastic carcinoma in 18, follicular carcinoma in 12, and papillary carcinoma in 17 cases. Roentgenograms of the neck were made with the patient erect in the anteroposterior and lateral positions. For lateral views the cassette was placed on the side of the greatest protrusion of the tumor, the bottom edge of the cassette being I inch below the sternoclavicular joint. The exposure factors were 110 kv., 3 mas., and a distance of 6 feet. Roentgenograms of the

† Assistant Professor, Department of Medicine.

<sup>\*</sup> Head, Section of Diagnostic Radiology, Universidad del Valle, Facultad de Medicina, Cali, Colombia, S. A.

chest were obtained in the posteroanterior projection. The shape of the trachea, its deviation from the normal position in an anterior and lateral direction or evidence of invasion or distortion of the tracheal wall, in addition to calcification and shape of the cervical tumor, were evaluated in all patients. Barium examination was used to evaluate invasion of the esophagus in patients with dysphagia. Chest roentgenograms were studied carefully for metastases and substernal extension of the cervical mass.

#### RESULTS

#### BENIGN TUMORS

In the majority of benign tumors, the degree of lateral displacement of the trachea was found to be proportional to the size of the tumor. A solitary parenchymatous nodule of the pyramidal lobe, located in the midline of the neck, did not produce lateral deviation of the trachea. Of 5 tumors less than 70 gm. of estimated weight, only 1

was associated with significant lateral displacement. Lateral deviation of the trachea clearly outlined the shape of the tumor. It was possible to determine the location of the upper part of the deviation, as well as the point at which the trachea returned to its normal position. In spite of marked displacement, the wall of the trachea was smoothly indented or had a normal diameter; there was no evidence of invasion. Only in I case with a large diffuse goiter due to bacterial thyroiditis, was there roentgenologic evidence of tracheal wall infiltration. Anterior displacement of the trachea was found in only 2 cases; I was a huge colloid goiter and the other bacterial thyroiditis. In all cases of a parenchymatous nodular goiter, the retrotracheal space appeared to be normal. Seventy-three per cent of all patients with benign tumors showed calcification. These were annular in shape, showing well defined borders and great radiodensity. Often there were large calcified masses (Fig. 1, A and B). The shape of the

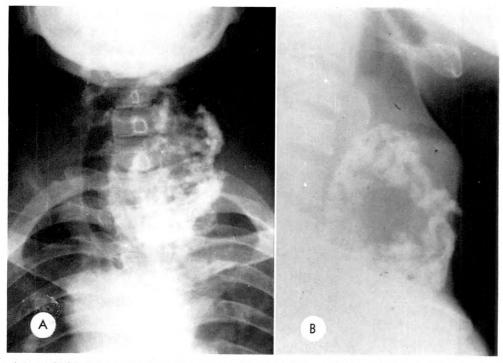


Fig. 1. (A and B) Nodular parenchymatous goiter showing dense annular calcifications. Displacement of the trachea is proportional to the size of the tumor. There are no changes in the caliber of the trachea. The upper and lower limits of displacement from the midline position are readily visible.

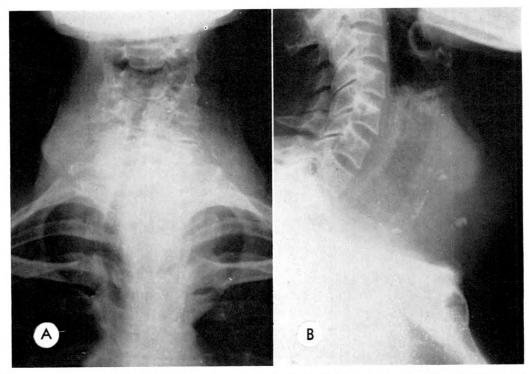


Fig. 2. (A and B) Anaplastic thyroid carcinoma and nodular parenchymatous gciter. There is a right cervical mass. The trachea is drawn toward the tumor. Calcifications are of the benign type.

calcification corresponded to that described by Holtz and Powers in benign thyroid tumors; however, there was I case of parenchymatous nodular goiter in which calcifications characteristic of those described for malignant tumor were found. Histologically, calcifications were noted in areas of necrosis and hemorrhage.

#### MALIGNANT TUMORS

We found 3 distinct patterns of tracheal changes in malignant tumors. In 31 per cent of the carcinomas, there was no lateral displacement, despite estimated weights of more than 70 gm. and asymmetric locations. In 1 patient the trachea was drawn toward the tumor (Fig. 2, A and B). When there was lateral displacement of the trachea, this was not proportional to the size of the tumor, often being of only slight degree in comparison with the huge cervical masses. In the malignant tumors producing tracheal deviation, the upper and lower limits of the tracheal deviation were difficult to determine since the tracheal shadow did not outline the cervical tumor clearly. The displaced trachea often showed an irregular narrowing of caliber due to invasion and torsion (Fig. 3, A and B). Anterior displacement in which the retrotracheal space was more than 1.5 cm. in diameter was found in 19 per cent of the malignant tumors (Fig. 3, A and B; and 4, A and B). Thirty-five per cent of all patients with thyroid carcinomas showed calcifications of the same type as found in benign tumors. All these cases had goiter associated with malignant thyroid tumors. Pathologic examination of the specimen revealed the calcifications to be located in the goitrous tissue. In 6 per cent there were poorly defined calcifications which were cloudy in appearance and of varying density; this type of calcification has been previously described in carcinomas by Holtz and Powers.5 Two of these patients had anaplastic carcinomas and I a papillary carcinoma. In I case of an anaplastic carcinoma with osseous metaplasia (Fig. 5, A and B), calcifications similar to those seen in sarcomatous tumors of the bones were found. Paralysis of the vocal cord was noted in I

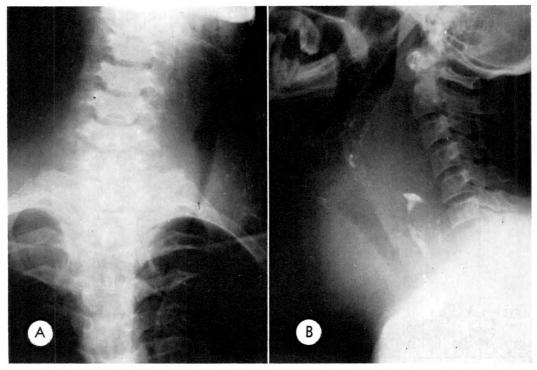


Fig. 3. (A and B) Follicular thyroid carcinoma and nodular parenchymatous goiter. Extensive anterior and lateral deviation with changes in the caliber of the trachea. The upper and lower limits of the displacement cannot be visualized.

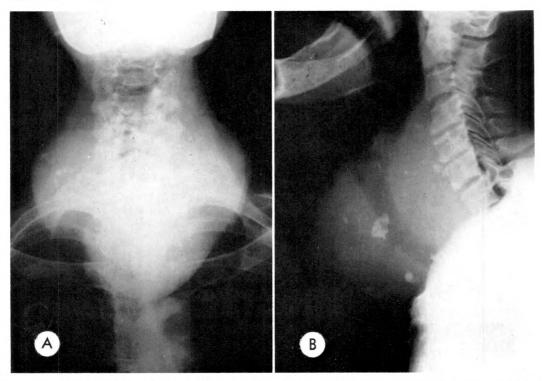


Fig. 4. (A and B) Anaplastic thyroid carcinoma and nodular parenchymatous goiter. Thyroid tumor located in the anterior neck. There is no lateral deviation in the presence of a large midline mass. The lateral view shows anterior displacement, changes of the tracheal caliber and benign calcification.

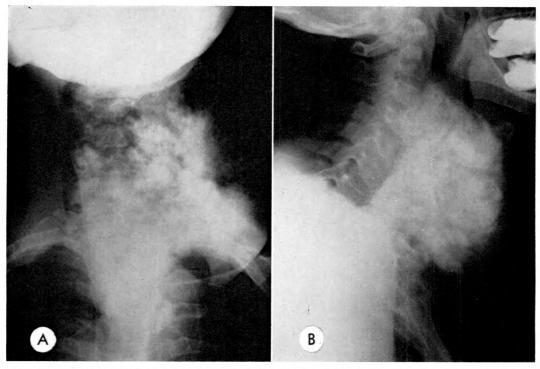


Fig. 5. (A and B) Anaplastic thyroid carcinoma. Extensive lateral deviation of the trachea as seen in benign tumors. However, there is extensive calcification resembling calcifications seen in sarcomas of the bones.

case (Fig. 6, A and B). A summary of the roentgenographic findings including incidence of metastasis is given in Table 1.

#### COMMENTS

Soft tissue roentgenograms of the neck in two planes did not facilitate the diagnosis of thyroid cancer in patients with small cervical masses due to parenchymatous nodular goiter, colloid goiter, thyroiditis or thyroid carcinoma. However, in tumors more than 70 gm. of estimated weight (Grade III and IV of the International Classification<sup>11</sup>), roentgenograms of the neck were found to be a valuable adjunct in the diagnostic armamentarium of the physician faced with the differential diagnosis of thyroid cancer and goiter.

A list of roentgenographic signs and type of tracheal displacement found to be of value is presented in Table II. In the interpretation, however, certain limitations must be emphasized. Only lateral and anteroposterior roentgenograms of the

neck, made by the technique described, were found to give optimal results. Roent-genograms of the chest, which frequently show only the inferior part of the neck, were inadequate for interpretation.

Diffuse colloid goiters of large size or with thyroiditis could be distinguished only with difficulty from carcinoma by roent-genographic signs alone. Anterior displacement of the trachea and invasion were seen in these patients as well as in patients with thyroid carcinoma.

In patients with nodular masses of the neck not due to thyroiditis or colloid goiter and weighing more than about 70 gm., the differential diagnosis was aided significantly by roentgenographic examination of the neck. Anterior displacement and invasion of the trachea were found in 19 per cent and 33 per cent respectively in thyroid carcinomas, but not in nodular goiters. The presence of fine, ill-defined calcification was found to be highly suspicious but not diagnostic for thyroid carcinoma. In 1 case of

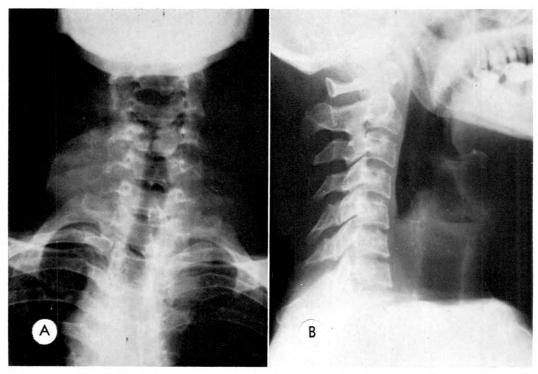


Fig. 6. (A and B) Anaplastic thyroid carcinoma. There is no deviation of the trachea in spite of a large predominantly right cervical mass. Paralysis of the left vocal cord suggests invasion by a malignant tumor.

 $Table\ I$  roentgenographic findings in 48 patients with thyroid carcinoma and 28 patients with nodular or diffuse goiter, pathologically verified, seen in 1959–1964 at the university hospital in call, colombia

	Thyroid (	Carcinoma	Nodular or Diffuse Goiter		
	No. of Patients	Per Cent	No. of Patients	Per Cent	
Tracheal Signs					
Anterior displacement	9	19	2	7	
Lateral displacement proportional to the size of the mass	12	25	11	40	
Disproportionately small displacement in presence of a large tumor	15	31	3	ΙΙ	
Invasion and distortion Cervical mass	16	33	1*	4	
Benign calcification	19	35	19	69	
Malignant calcification	3	6.4	I	4	
Esophagus	3				
Invasion	2	4.2			
Other Organs					
Pulmonary metastasis	19	35			
Bony and other metastasis	4	8			

<sup>\*</sup> Thyroiditis.

Table II
ROENTGENOGRAPHIC SIGNS IN THYROID TUMORS

Malignant Tumors	Benign Tumors				
<ol> <li>Tumor</li> <li>Tracheal changes</li> <li>Invasion of esophagus</li> <li>Vocal cord paralysis</li> <li>Calcification</li> <li>Pulmonary metastasis or metastasis to other organs</li> </ol>	1. Tumor 2. Tracheal displacement 3. Calcification				
TRACHEAL DISPLACEMENT I	N THYROID TUMORS				
Malignant Tumors	Benign Tumors				
<ul> <li>a. Displacement not proportional to the size of the tumor</li> <li>b. The upper and lower limits of the displacement not usually well defined</li> <li>c. Diminution of tracheal diameter</li> <li>d. Anterior displacement</li> </ul>	a. Displacement proportional to the tumor size     b. The upper and lower limits of the displacement usually well defined     c. Normal tracheal diameter				

parenchymatous nodular goiter, this type of calcification was found and represented probably an early stage of the benign type calcifications. Disproportionately little displacement of the trachea in the presence of a large mass was found more frequently in thyroid carcinomas. Due to the frequent association of thyroid cancer with goiter, 9,10 benign type calcification was found in 35 per cent of thyroid tumors. Roentgenograms of the chest and the bony skeleton were helpful in the presence of metastasis.

#### SUMMARY

The value of soft tissue roentgenography of the neck in patients with thyroid disease from an endemic goiter area was studied. In 47 patients with thyroid carcinoma, 21 with nodular parenchymatous goiter, 5 with colloid goiter and 2 with bacterial thyroiditis, soft tissue roentgenography facilitated the differential diagnosis only in tumors more than 70 gm. of estimated weight (Grade III and IV). It was found to be more difficult to distinguish colloid goiter and thyroiditis than nodular goiter from carcinoma by roentgenologic signs alone. Invasion of the trachea, anterior displacement of the trachea, calcifications, and small lateral displacement of the trachea in the presence of a large cervical mass were of value in the differential diagnosis in this sequence.

Heinz W. Wahner, M.D. Departamento de Medicina Interna Universidad del Valle Cali, Colombia, S.A. Apartado aereo 2188

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# THE RATE OF GROWTH AND NATURAL DURATION OF PRIMARY BRONCHIAL CANCER\*

By L. HENRY GARLAND, M.D., B.Ch., M.D. (Hon.) san francisco, california

KNOWLEDGE of the natural duration and rate of growth of cancer is desirable for progress in its diagnosis and treatment "during the useful period," i.e., during the time prior to which it has spread. Rate of growth is recognized as a useful clue in the prognosis of cancer in general, slow-growing tumors (even though large and clinically "late") usually having a better prognosis than rapidly growing tumors (even though small and ostensibly "early").\frac{1}{2.8}

Peripherally growing primary bronchial tumors, when untreated for one reason or another, offer unique opportunities for determining the rate of growth of spontaneous human cancer under natural conditions, providing that adequate serial roent-genograms have been made and are available for study. Two years ago, we reported a series of 41 such cases, 40 of which provided measurable data.<sup>3</sup>

This paper is a report of an additional series of patients with primary bronchial cancer, on whom 2 or more sets of roent-genograms were available, and in whom microscopic diagnosis was ultimately established.

#### MATERIAL AND METHOD

Nineteen patients from one or more of 5 hospitals\* in San Francisco were available for study. They had solitary, peripheral nodular pulmonary lesions, subsequently verified as primary bronchial carcinoma.

The tumor was measured in 2 or more dimensions in posteroanterior and lateral teleroentgenograms, and the "average" diameter was recorded for purposes of comparison with subsequent studies. As pointed

out by Collins and others,<sup>2</sup> when the diameter doubles, the volume increases eight-fold.

The "diameter" was then recorded on a semilogarithmic growth rate chart, from which either the volume doubling time or the average slope of growth could be obtained. The former (volume doubling time) has been extensively described.<sup>2,3,9,10</sup> The latter (average slope of growth) has not previously been stressed, and may prove to be a simple and useful method of expressing the probable duration of a given tumor, at least for those tumors not over about 2 cm. in diameter.

The method is illustrated in Figures 1, A, B and C; and 2.

#### RESULTS

For purposes of brevity, the 19 patients reported for the first time in this paper are divided into 2 groups: (a) patients with squamous cell carcinomas and undifferentiated carcinomas, and (b) patients with adenocarcinomas.

There were 14 cases with squamous or undifferentiated carcinomas. The calculated duration of growth from 1 cell size to a tumor 2 cm. in diameter in this group ranged from 2.5 years to 14.5 years. The median duration was 8 years.

There were 5 cases with adenocarcinomas. The calculated duration of growth to a tumor 2 cm. in diameter ranged from 3.25 to 72 years. The median duration was 15 years.

The age range of the patients was 43 to 78 years. All but one were male. The details of growth rate and duration are shown in Tables 1 and 11.

In Figures 3 and 4 (previously unpublished) a summary is given of the observa-

<sup>\*</sup> San Francisco General, St. Joseph's, Letterman Army, French, and Southern Pacific Hospitals.

<sup>\*</sup> From the Department of Radiology, The University of California, San Francisco General Hospital, San Francisco, California.

tions in the 40 patients reported in our first paper. Note that the data have been calculated to a tumor size of approximately 2 cm. diameter. (Most of the lesions were

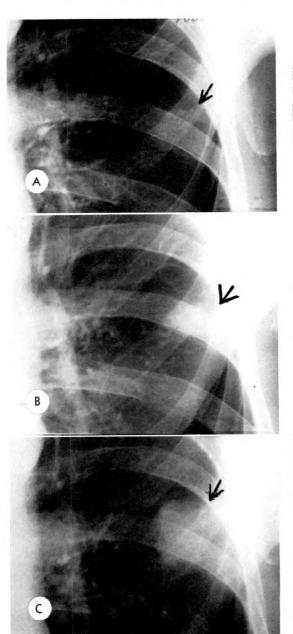


Fig. 1. Example of a peripheral nodular lesion in male, aged 62, without symptoms. (A) Lesion approximately 1 cm. in diameter in March, 1956. (B) Lesion approximately 1.9 cm. in diameter in March, 1958. (C) Lesion 4 cm. in diameter in June, 1959. Biopsy revealed squamous cell carcinoma.

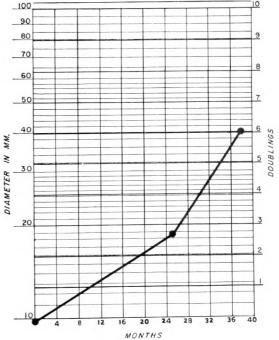


Fig. 2. Semilogarithmic growth rate chart based on measurements of case shown in Figure 1, A, B and C. The volume doubling time may be estimated by dropping vertical lines from the growth curve to intersect any adjoining pair of "doubling lines." In this case the doubling time averaged 6.7 months. The estimated duration from "I cell size" to a tumor 2 cm. in diameter is 17 years. (Lobectomy was performed in 1959, when the tumor was 4 cm. in diameter.)

larger at the time of microscopic validation; corrections were made to the point at which their curves crossed the 2 cm. diameter line on the growth rate charts previously published.<sup>3</sup>)

The results in the cases reported in this paper are similar in general to those reported in our earlier work.<sup>3</sup> Combining these 19 cases with the prior 40 measurable cases, we find that the median duration of a peripheral squamous or undifferentiated bronchial cancer 2 cm. in diameter is about 8 years, and of an adenocarcinoma about 16 years. The range is considerable (Table III).

#### SLOPE OF GROWTH RATE CURVE

The individual growth rate curves for the first 40 patients have previously been re-

Table I

GROWTH OF PERIPHERAL NODULAR PRIMARY CARCINOMAS REPORTED IN THIS PAPER

(as shown by average diameter in cm.)

Case No.	Date	Size	Date	Size	Date	Size
1 (42)	3/58	0	5/60	0.5	5/62	1.75
2 (43)	3/55	0.14	11/59	1.3	3/63	2.3
3 (44)	3/60	I.I	12/60	2.5	11/61	3.5
4 (45)	9/61	0	6/62	1.0	12/62	2.2
5 (46)	8/58	0	1/60	0.9	3/63	3.7
6 (47)	4/59	0.8	11/59	I.4	10/61	4.5
7 (48)	7/53	0.9	1/59	2.0	8/60	4.0
8 (49)	12/58	o ´	3/59	0.5	7/59	1.0
9 (50)	6/60	0	7/61	1.5	9/62	2.0
10 (51)	6/62	0	8/63	3.6	10/63	4.I
11 (52)	9/62	1.0	8/63	3.5	9/63	4.2
12 (53)	4/62	0	10/63	2.0	11/63	2.2
13 (54)	3/59	0	2/64	3.5	3/64	4.0
14 (55)	3/58	0	3/62	0.5	5/64	4.5
15 (56)	9/60	2	2/64	2.5	4/64	3.4
16 (57)	11/63	1.0	4/64	3.0		
17 (58)	1/60	0.9	5/60	1.1	12/61	3.c
18 (59)	8/58	0.7	10/60	1.3	1/62	2.4
19 (60)	5/59	0.8	8/60	1.5	7/62	4.0

ferred to. As with the present series of patients, when there is a sufficient number of points recorded for the individual case (e.g., Case 19 of Series 1), the general slope of the curve may reasonably be measured (it is approximately 50° for that particular case). Establishment of such a slope when only 2 points are available is admittedly fraught with error (Fig. 5). However, it seemed to be of interest and potential value to calculate the slopes of all cases recorded by the author and to plot same against time. Figures 6 and 7 illustrate the findings. It is obvious that the longer the duration of recorded growth, the greater the range in potential growth time.

It is emphasized that, in attempting to use such "slope curve," it is desirable to have at least 3 measured points, each preferably at least 3 months apart. The curve tends to be more valid for tumors not over about 2 cm. in diameter. Calculations are based on the assumption that the curve transects the junction of the abscissa and ordinate; simple corrections may be made when such is not the case, by adding or subtracting the number of months by which the line "misses" the transection point.

#### DISCUSSION

It has been emphasized and it should be repeated that exponential growth is not necessarily present over the entire life-time of any given tumor, but it is believed to be reasonably well established that for tumors of moderate size (in the case of primary bronchial cancer, tumors up to 2 cm. in average diameter) it occurs over a signifi-

**₩** 

Fig. 3. Estimated duration of growth in years of a series of 22 cases of squamous cell carcinoma of the bronchus from the time the tumor was a theoretical size of 1 cell to the time it was a peripheral tumor 2 cm. in diameter.

Table II

ANGLE OR SLOPE OF GROWTH RATE AND DURATION
OF GROWTH OF TUMOR IN PATIENTS
REPORTED IN THIS SERIES

Case No.	Slope in Degrees	(a) Duration Growth to Time Turn Averages Would Aven 2 cm. in Dia	the mor or erage	Roent	phic eter at Tumor
I	52	10.25 y	Τ.	1.75	cm.
2*	II	,	r.	2.3	
3	60	8.5 y		3.5	
4	77	2.5 y		2.2	
5	43	14.5 y	r.	3.7	cm.
6	53	11.0 y	r.	4.5	cm.
7	55	9.5 y	r.	4.0	cm.
8*	75	3.25 y	r.	1.0	cm.
9	45	14.5 y	r.	2.0	cm.
Ю	75	3 y	r.	4.1	cm.
11	71	4.8 y	r.	4.2	cm.
12	61	7.25 y	r.	2.2	cm.
13	64	7·3 y	r.	4.0	cm.
14*	65	6.0 y	r.	4.5	cm.
15*	10	72 y	r.	3.4	cm.
16	78	2.5 y	т.	3.0	cm.
17	51	12 y	r.	3.0	cm.
18*	45	14.5 y	r.	2.4	cm.
19	51	12 y	r.	4.0	cm.

<sup>\*</sup> Adenocarcinoma. All others were squamous cell carcinoma or undifferentiated carcinoma.

TABLE III

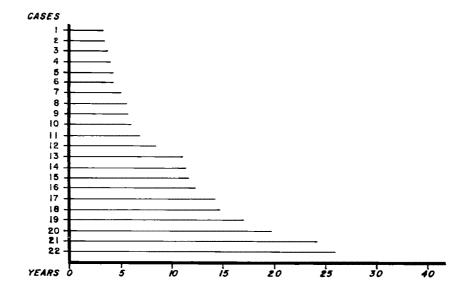
CALCULATED DURATION OF GROWTH OF PRIMARY BRONCHIAL CANCER FROM ITS INITIATION AS A THEORETICAL TUMOR THE SIZE OF I CELL (OR A SMALL "FIELD OF CELLS") TO THE TIME IT IS A TUMOR 2 CM.

IN AVERAGE DIAMETER

Histologic Type	No.	Duration in Y	of Growth
0	Cases	Median	Range
Squamous, Undif- ferentiated and Mixed Carcinoma	48	8	2.6-36
Adenocarcinoma	11	16	2.3-72

cant portion of the tumor's lifetime in a majority of cases.\* When bronchial tumors grow larger than 2 or 3 cm. in size, their growth curves not infrequently bend towards the time axis. Many observers have found that a wide variety of tumors give linear plots of diameter versus time. 1.5,9,10 Growth may be more rapid when only a few hundred cells are involved, and slow down when several billions are present. However, it should be noted that most statements on growth pertain to tumors (experimental or clinical) measured in only

<sup>\*</sup> Rare examples of delayed growth have been reported in 5 patients by Hughes and Blades, Postgrad. Med., 1960, 28, 616.



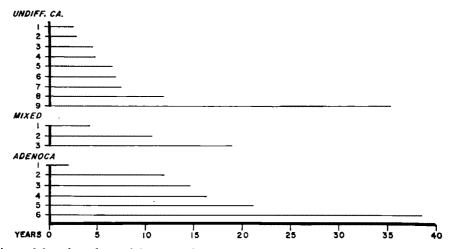


Fig. 4. Estimated duration of growth in years of a series of 9 cases with undifferentiated bronchial carcinoma, 3 cases with mixed adeno-squamous cell carcinoma and 6 cases with adenocarcinoma. Measurements from the time the tumor was a theoretical size of 1 cell to the time it was a peripheral tumor 2 cm. in diameter.

2 diameters; pulmonary nodular carcinomas are unique in permitting 3 dimensional measurements *in vivo*—and in some cases, over long periods of time.

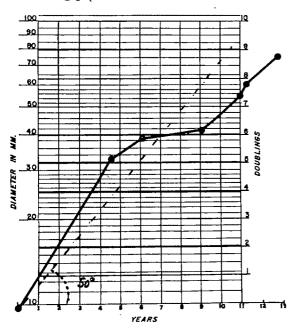


Fig. 5. Growth rate curve of Case 19 from Series 1. Note that the time scale in this one instance is in years and not months. Superimposed on the growth rate curve is the approximate linear slope thereof—about 50 degrees in this case. This would indicate a growth duration of some 35 years to the time when this particular tumor was 2 cm. in diameter.

It has also been emphasized that many peripheral nodular cancers consist not just of a collection of cancer cells, but of cancer cells plus stroma, necrosis, hemorrhage and so forth. Such non-neoplastic tissue does not usually constitute the bulk of any tumor under 2 cm. in diameter. In larger tumors, it may do so but even when it does, Spratt, Spjut and Roper<sup>10</sup> believe that the basic premise in making the type of growth determinations recorded in this paper is not vitiated.

We have shown previously that, assuming the average human bronchial cancer cell to be about  $25 \mu$  in diameter, only a single volume doubling separates a 2 cm. nodule that is composed entirely of cancer cells, from one composed about one-half of cancer cells and one-half of stroma.

Estimated number of cancer cells in a solitary nodule 2 cm. in diameter

- a. Composed of cancer cells only:
- 512 million cancer cells (29 volume doublings)
- b. Composed of equal proportions of cancer cells and stroma:
- 260 million cancer cells (28 volume doublings)

We are currently studying the relative proportions of tumor cells and stroma in those nodules which were removed while still less than 2 cm. diameter.

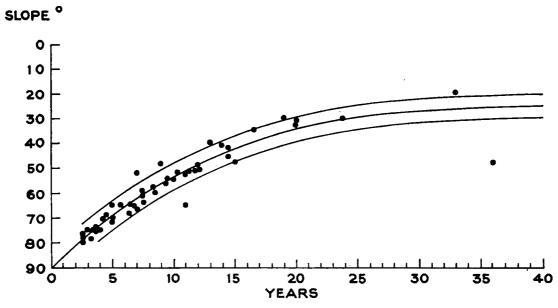


Fig. 6. Chart showing relationship of slope of growth rate curve and estimated duration of tumor in years. The dots indicate 48 bronchial carcinomas of squamous cell or undifferentiated type.

In closing, it is desirable that credit again be given to Mottram<sup>6</sup> for demonstrating the thesis of this paper 30 years ago—in connection with studies on mouse cutaneous epitheliomas. His diagram (Fig. 8) tells the story. His text is worth repeating, in part: "In a previous paper, consideration was given to the possibility that these tar warts had their origin from single cells, and it was seen that the natural history of the warts accorded well with this proposition. In the case of a wart doubling its area in

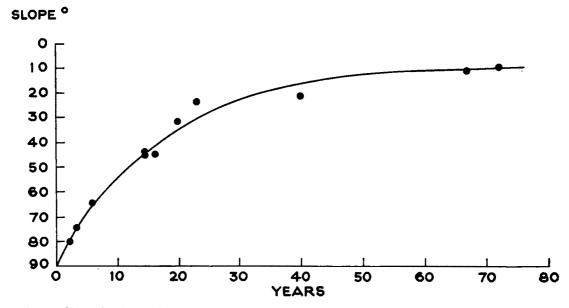


Fig. 7. Chart showing relationship of slope of growth rate curve and estimated duration of tumor in years. The dots indicate 11 primary bronchial carcinomas of adenocarcinoma type.

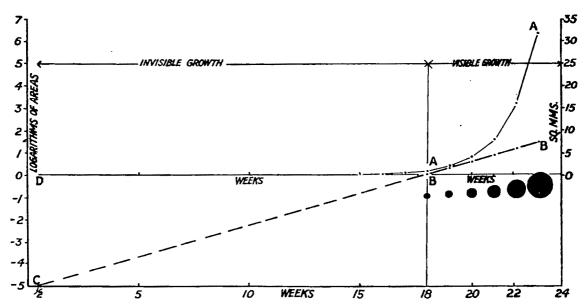


Fig. 8. Diagram illustrating the preclinical, or previsible, and the clinical phases of a cancer. The series of black circles on the right are the measured areas of a mouse epithelioma that was fast growing, doubling its area each week. The curved line A-A shows the visible growth over a period of 5 weeks, the scale on the right being in square millimeters. The tumor grew from 1 to 32 sq. mm. in that time. Below the curved line A-A is the straight line B-B that is based on the logarithms of the areas of the epithelioma. By projecting the line B-B backward to meet the theoretical 1 cell size level, it is evident that the preclinical phase lasted for about 18 weeks, assuming a fairly constant growth rate. The line is shown as B-C. C is during the period of carcinogenic tar application. The scale on the left represents the logarithms of the areas. (Reproduced by permission.<sup>6</sup>)

one week, it was shown that, if it arose from a single cell, about ten weeks would be required for the appearance of a visible wart. It follows, that if within a slow-growing wart a group of fast-growing cells arises, taking origin from a single cell, then many weeks will be required before these fastgrowing cells will form a large proportion, say half, of the wart. When, therefore, an increased upward concavity in the growth rate of a wart is observed, it represents not a change immediately occurring but one which had occurred many weeks previously when the wart was still invisible and one of its cells assumed a faster rate of growth; this, of course, on the assumption that groups of fast-growing cells within warts arise, like the warts themselves, from single cells."7

The applicability of the observations and conclusions of this paper to other non-peripheral nodular forms of bronchial cancer has been discussed previously.<sup>3</sup> It has

been our conclusion and is still believed that they are applicable to the majority of primary bronchial carcinomas, whether central or peripheral, at least for those tumors less than large or multicentric (i.e., less than about 5 cm. in average diameter).

Unfortunately, the clinical utility of these observations in terms of cancer prevention or treatment is still modest. Further, it is desirable that one always bear in mind the distinction between (a) the true total duration of a given cancer, and (b) the duration of its diagnosable phase. Most bronchial cancers have passed some three-fourths of their true total duration before they become diagnosable by methods currently available.

#### COMMENT

Assuming (as I believe is reasonable) that similar long growth times occur with many other forms of human cancer, it would appear overdue that we should re-

vise the wording of our propaganda for socalled early diagnosis. Support might likewise be increased for research in practical methods of assaying the biologic potential of individual tumors at the time of microscopic diagnosis.<sup>4</sup>

#### SUMMARY

An additional series of 19 patients confirms the growth rate findings reported in an earlier series of 40 patients with primary untreated bronchial cancer.

The duration of growth of this type of cancer is much longer than has previously been believed. For example, an "average" peripheral squamous cell cancer requires approximately 8 years to reach a diameter of about 2 cm., and a peripheral adenocarcinoma requires about 16 years to reach that size.

It is probable that during this long phase (most of it pre-clinical, and not recordable on standard roentgenograms), metastasis occurs, rendering this tumor so difficult to eradicate.

Department of Radiology The University of California San Francisco General Hospital San Francisco, California

My thanks are due to the many colleagues who have helped with the collection and analysis of the cases listed in this series, especially the pathologists at the several San Francisco Hospitals. Support was kindly available in part from the California Division of the American Cancer Society and the William Hume Cancer Research Fund.

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# SOME CONSEQUENCES OF PULMONARY IRRADIATION\*

### A SECOND LONG TERM REPORT

By DAVID TEATES and GEORGE COOPER, Jr. MEMPHIS, TENNESSEE

THIS paper presents an evaluation of the long term effects of irradiation of the lungs in patients with thoracic malignant disease.

#### REVIEW

In a previous report, we commented upon the short term effects.2 Using 3 tests, timed vital capacity (VC), maximum breathing capacity (MBC), and arterial oxygen (AO) percentage saturation, we studied the physiologic function of the lungs before, during, and after pulmonary irradiation incident to treatment of carcinoma of the breast, lung, and several miscellaneous malignancies. During the same period, serial roentgenography and careful clinical evaluations were carried out. We reported our observations when the study had been underway for 15 months, and were able to present useful data on 28 patients.

We confirmed some previous observations of others and drew the following conclusions:

- I. The degenerative and fibrotic changes produced by irradiation in all tissues are of especial significance when they occur in tissues where their presence interferes with vital functions. One of those in which this happens is pulmonary tissue, irradiation injury of which impairs the ventilatory and diffusion capacities of the lung.
- 2. Because the enormous reserve capacity of the lungs provides a good margin of safety, when care is taken to minimize incidental pulmonary irradiation and when the lungs are normal or had been normal before a primary pulmonary malignancy developed, the doses of radiation usually recommended can probably be given with

sequelae of acceptable frequency and severity. The short term effects have been fairly well documented; the long term effects have not.

- 3. When the pulmonary reserve has been lowered by pre-existing abnormality, less radiation can be tolerated.
- 4. Serial physiologic testing increases the accuracy with which radiation effect can be evaluated. There is some hope that it may be helpful in treatment planning and guidance.<sup>2</sup>

As far as we know, these data from 28 patients, though a small collection, are actually the largest of its kind yet reported. The reasons are several. Lung cancer is a frequent thoracic malignancy, but many of the patients suffering from this disease deteriorate too rapidly for the accumulation of serial data. Many of those who have lung cancer or some other thoracic malignancy and who survive for longer periods are not physically able to undergo the tests of physiologic evaluation; and of those who can, some are not willing. Therefore, the accumulation of significant data is difficult and slow.

#### MATERIALS AND METHODS

In this report are included data on 16 patients for periods up to 40 months after thoracic irradiation. Five cases were presented in an incomplete form in the previous report.<sup>2</sup> We continued to use the methods of study and approach to radiation therapy as described in the previous report. The breast cancer patients usually received 3,100-4,100 r tissue dose in 24-40 days at a 3-5 cm. depth in the supraclavicular, axillary and internal mammary lymph node regions delivered with a Co<sup>60</sup> unit.

<sup>\*</sup> Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28-October 1, 1965.

Using roentgen rays with a half value layer of 6 mm. Al, an additional dose of 1,800–2,000 r in air was delivered to the chest wall over a period of 11–18 days in 80 per cent of the cases. The lung cancer patients received 4,500–5,500 r tumor dose in 36–44 days delivered with a Co<sup>60</sup> unit. One patient (MKT) received 3 courses of thoracic irradiation during the 3 years of observation; all other cases had only a single course to the chest.

The patients tolerated therapy well. Seven developed a cough during or shortly after therapy; 2 of these patients had bronchogenic carcinoma. Two patients developed dyspnea on exertion to a mild degree and of short duration. One patient with bronchial carcinoma and another who developed a chronic pleural effusion secondary to pleural metastasis from the breast had more troublesome dyspnea. One patient (MKT) developed pleuritic pain on 2 occasions without evidence of septic illness; she later developed recurrent breast tumor, and the etiology of the pain is uncertain. A number of patients developed weakness, anorexia, and other symptoms of systemic radiation effect.

Eight patients developed roentgenographic evidence of radiation reaction. Five of these were cases of bronchial carcinoma in which it was frequently difficult to determine the extent of tumor involvement and radiation reaction. Roentgenographic evidence of lung damage was found in 3 patients who received irradiation for carcinoma of the breast. One of these patients developed a chronic pleural effusion thought to be due to recurrence rather than irradiation. Table I shows the cases which developed significant roentgenologic changes.

The physiologic data are also presented in Table I. Only 2 patients (NS, FP) with breast cancer developed significant post-irradiation reduction in vital capacity and maximum breathing capacity. One of these patients had the pleural effusion previously mentioned. Three additional patients (EMS, ECH, and MT) developed arterial desaturation at the conclusion of irradiation or 3

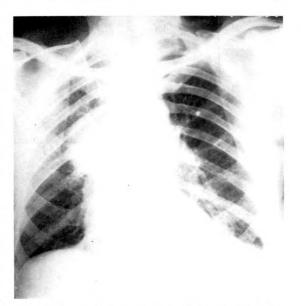


Fig. 1, Case 1. Roentgenogram of the chest prior to irradiation. A mass is evident in the right root zone.

months post irradiation. None of the latter group had significant roentgenographic changes.

The patients being treated for lung cancer frequently showed improved ventilatory capacity and arterial saturation following irradiation. Three of these patients later had reduction of function; whether the reduction is related to tumor activity or fibrosis is uncertain.

The selected case reports which follow illustrate the correlation of roentgen and physiologic data.

#### REPORT OF CASES

Case I (DAK). This 75 year old man was found to have a right hilar bronchial carcinoma in October, 1960. A tumor dose of 5,500 r was delivered to the right hilus and mediastinum in 30 days. As noted on the roentgenograms (Fig. I and 2), the mass promptly resolved. Serial examinations demonstrated radiation reaction at 3 months which did not progress after 6 months (Fig. 3). Pulmonary function studies showed marked improvement during therapy. The functional values did not change as the roentgenographic evidence of pneumonitis developed. The patient died 21 months after therapy with brain metastases.

Case II (FP). This patient received 3,400 r at a depth of 5 cm. to the supraclavicular and

**FABLE I** 

	Predicted Values	Values	Values PI	Values at 3 mo.	Values at Values at Values at 3 mo. 9 mo.	Values at 9 mo.	Values at 12 mo.	Values at 18 mo.	Values at	Values at 30 mo.	Values at 36 mo.	Values at	Values at
ALS: carcinoma of left breast	VC 2.8 VC(3) MBC 83.6 AO	3.8	3.9 3.7 98.4 93.4	3.9 3.8 97.5 92.5	3.9 3.6 103.6	4.0 3.6 130.1		4.1(15 mo.) 3.7 131.5 93.7	4.2(21 mo.) 3.7 105.0 94.9				
MT: carcinoma of right breast	VC 2.9 VC(3) MBC 89.1 AO	3.2 3.0 1 61.0 93.1	3.6 3.4 98.4 91.6	2.2 2.4 4.4 6.8 8	3.7	3.4 3.3 99.0 2.19	3.8 87.6 90.1	3.3 3.1 85.0 92.0	3.5 3.0 87.1 90.4	3.6 3.1 90.9			
LEA: carcinoma of left lung	VC 3.6 VC(3) MBC 99.1 AO	6 4.3 3.4 1 102.9 92.5	3.8 116.2 92.4	3.6* 3.5 112.7 93.5	4.2* 3.9 110.5 95.2	4.1* 3.4 106.9 93.7	\$.50 4.50 6.40	3.8* 3.4 93.7 94.0	4.2* 3.0 85.7 90.3	3.6*	4.4* 3.3 83.4 90.1		
MKT: carcinoma of right breast	VC 3.7 VC(3) MBC 73.8 AO	7 2.8 8 95.6 93.4	3.1 77:4 91.3	3.0 2.9 81.9 93.5	9.4 91.0 94.3	3.0 2.9 88.5 95.4	3.1 105.2 94.0	3.1 2.9 84.5 93.4	3.0 2.9 108.1	3.0 2.8 105.3 94.1	2.9(33 mo.) 2.7 99.9 93.3	3.1(37 mo.) 2.8 95.5 94.4	3.0(40 mo.) 2.8 98.3 93.3
FP: carcinoma of left breast	VC 2.4 VC(3) MBC 71.0 AO	4 1.8 0 67.0 91.7	1.8	8.8 89.8	1.8* \$5.1 93.3		1.8* 38.4 94.5	1.8(15 mo.)* 53.4 95.7	1.8* 45.3 93.9	1.7*			
GB: carcinoma of right breast	VC 2.7 VC(3) MBC 73.4 AO	7 3.3 3.0 4 89.1 95.1	3.1 81.5 94.0	2.9 2.7 89.0	2.8 2.7 93.6	3.0 9.9 5.49	3.0 2.8 84.9 95.1	2.9 7.2.1 7.2.1 2.49	2.9 2.7 85.9 95.8	3.1 2.97 79.2	2.9 2.6 2.77 2.59		
EMS: carcinoma of left breast; asthma	VC 2.8 VC(3) MBC 78.9 AO	8 I.5 9 26.7 92.8	1.7 1.3 32.3 92.4	7.7 7.0 7.0 8.88	1.5 0.1 0.8 0.5 2.5	2.1 1.3 36.6	9.0 4.1 4.54 90.3	1.4 0.9 25.2 92.8	1.8 1.1 26.7 91.9				
DAK: carcinoms of right lung	VC 3.4 VC(3) MBC 86.7 A0	4 2.6 7 37.7 83.8	3.6 71.0 91.4	3.3* 65.0 93.2	3.3*	3.3* 82.9 90.7	3.3* 74.5 93.0						
DJR: carcinoma of right lung	VC 3.9 VC(3) MBC 97.4 AO	4 2.9 4 57.6 89.7	4.0 3.2 95.6	2.2 2.2 65.4 91.2									

	Predicted Values	Values AI	Values PI	Values at Values at Values at 3 mo. 6 mo. 9 mo.	Values at 6 mo.	Values at 9 mo.	Values at 12 mo.	Values at 18 mo.	Values at	Values at 30 mo.	Values at 36 mo.	Values at	Values at
ASM: carcinoma of left breast	VC 3.7 VC(3) MBC 82.8 AO	3.4 3.3 105.5 92.6	3.2 3.2 130.0 93.6	1.7* 100.7 92.7	2.9 2.9 110.1 93.0	2.9† 111.6 91.8	2.8† 118.0 93.0						Parameter Company
EBM: carcinoma of lung with superior mediastinal syn- drome	VC 3.5 VC(3) MBC 89.0 AO	23.4 28.4 90.8	2.8 46.2 92.0	1.9 1.9 90.0									
ECH: carcinoma of right breast	VC 2.6 VC(3) MBC 77.6 AO	2.5 2.4 68.6 92.4	2.4 2.3 79.7 87.0		2.3 2.2 74.2 93.3	2.4 2.2 79.2 93.4	2.3 2.1 68.6 93.2						
CAD: carcinoma of left lung	VC 3.6 VC(3) MBC 106.5 AO	4.1 4.1 108.7 92.8	3.7 113.8 92.3	3.7 3.5 96.1									
NS: carcinoma of left breast	VC 2.6 VC(3) MBC 76.2 AO	3.6 3.1 91.3	3.5 3.0 101.4	2.0 2.0 69.4	2.4 2.1 7.07	2.6 2.2 74.7	2.7(14 mo.) 2.2 74.9	1.7(20 mo.) 1.4 40.6	2.1(28 mo.) 1.8 62.0		I.5(34 mo.) I.2 4I.2		
CC: carcinoma of right lung	VC 2.4 VC(3) MBC 60.8 AO	2.9 2.7 61.3 92.4	2.9 2.8 84.2 92.1	2.0* 1.9 67.8 88.7	2.2* 2.1 69.7 92.2	2.1* 63.7 93.8	2.3* 68.0 93.8	2.4* 2.3 55.7 94.6	2.2 2.2 70.0 94.7				
MML: carcinoma of right breast	VC 3.0 VC(3) MBC 90.8 AO	4.0 3.8 105.2 95.0	3.6 98.0 92.7		3.4 3.1 105.9 94.6		3.5 3.4 103.8 91.8	3.6 3.4 118.4 92.6	3.8 3.7 109.9 93.3	3.3 3.3 129.5 94.0			

AI: before irradiation.

PI: after irradiation.

\* Radiation pneumonitis or fibrosis.

† Marked clearing of radiation reaction.

VC= vital capacity, in liters.

VC(3)= three-second timed vital capacity, in liters.

MBC= maximum breathing capacity, in liters.

AO= arterial-oxygen percentage saturation.

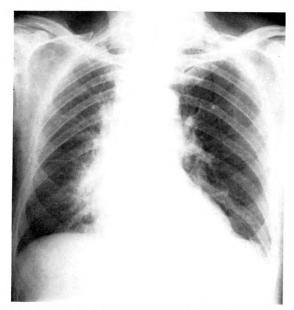


Fig. 2. Case I. Three months after irradiation, the mass has resolved but radiation reaction is evident.

axillary lymph nodes as part of a course of radiation therapy for adenocarcinoma of the left breast. Six months later a chest roentgenogram demonstrated an infiltrative process in the left apex (Fig. 4). Serial examinations over the following 4 years show no significant change (Fig. 5). Arterial oxygen desaturation developed 3 months after irradiation but had cleared by 6



Fig. 3. Case I. One year after irradiation, fibrosis is prominent with shift of the upper mediastinum to the right.

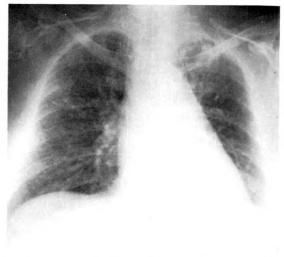


Fig. 4. Case II. Ten months following therapy to the mediastinum and supraclavicular lymph nodes, an infiltrative process is evident in the left apex.

months. No significant ventilatory change occurred.

Case III (CC). This patient received thoracic irradiation in October, 1959 for a poorly differentiated bronchial carcinoma of the right main stem bronchus. Figure 6A demonstrates deviation of the esophagus around the mass. The patient received 5,300 r tumor dose in 36 days with good tumor regression (Fig. 6B). Roentgenograms showed a pneumonitis at 3 months which reached a peak intensity at 6 months (Fig. 7A). The acute reaction subsided somewhat by 9 months (Fig. 7B), after which no significant roentgenographic change occurred (Fig. 8). A reduction of 30 per cent in the vital



Fig. 5. Case II. Three and one-half years after irradiation, there is little change in the appearance of the radiation reaction.

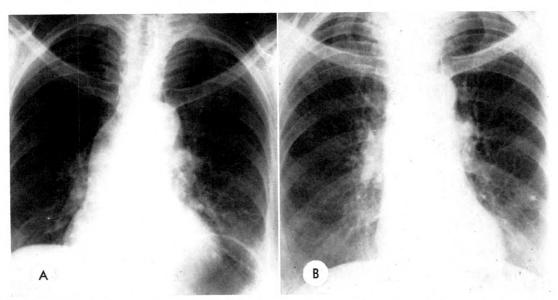


Fig. 6. Case III. (A) Prior to irradiation, a mediastinal mass is evident causing deviation of the barium column to the left. (B) At the completion of therapy, the mass is essentially cleared.

capacity occurred at 3 months associated with a significant hypoxemia. The arterial saturation subsequently improved. Twenty-eight months after therapy, the patient developed signs of tumor activity which resulted in her demise 5 months later.

#### DISCUSSION

Fifty per cent of the patients in this series

developed roentgenographic changes consistent with radiation reaction, although reactivation of tumor growth cannot be ruled out in some instances. Only 25 per cent of the patients developed significant reductions in ventilatory function. All of the patients with ventilatory disturbances also had roentgen evidence of damage, al-

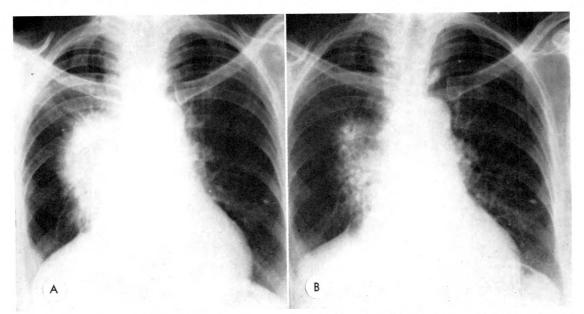


Fig. 7. Case III. (A) The radiation pneumonitis reached a peak intensity 3 to 6 months after irradiation. (B) Nine months after irradiation the acute reaction has subsided, but there is prominent fibrosis. The right diaphragm is elevated.

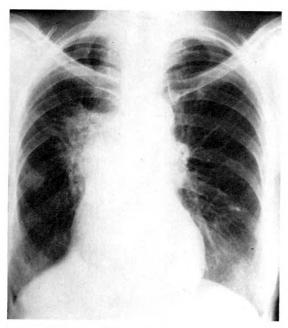


Fig. 8. Case III. There is little change at 2 years.

though there were 3 patients with hypoxemia who did not have abnormal roent-genograms.

Unfortunately, the measurement of physiologic functions is not an exact technique. Results are subject to variation due to the attitude and aptitude of the patient, the general well-being of the patient, and the skill and patience of the investigator. There is a tendency for the remaining normal lung to show compensatory changes in function with a resultant stabilization of total lung function. The compensatory functional change is noted in Case III which showed a severe reaction in a limited area with relatively little functional change. Recent experimental studies in dogs<sup>5</sup> have demonstrated marked regional changes in function of irradiated lung when the total lung function remained remarkably stable. For these reasons, physiologic function studies may not accurately reflect the changes that may be demonstrated in the roentgenogram.

Several patients in this study and in the previous report developed arterial oxygen desaturation. This change has been noted previously by others and has been explained several ways.

Recent experimental studies indicate that the hypoxemia is not the result of an alveolar-capillary block.5 In these studies, dogs were subjected to unilateral thoracic irradiation. Physiologic functions of each lung were frequently evaluated for 6 months after irradiation. A reduction in diffusing capacity occurred in the damaged lung after 6 to 10 weeks (Fig. 9), as measured by the steady state carbon monoxide method. A simultaneous reduction in pulmonary blood flow and ventilation of the damaged lung was measured by differential spirometric techniques (Fig. 10). Thus it appears that general pulmonary function is disrupted and the hypoxemia apparently results from mechanisms such as ventilation-perfusion abnormalities. Further studies are in progress in this area.

No patients in this series developed evidence of pulmonary damage later than 6 months after irradiation. Also, there was no significant decrease in functional capacity after 12 months with the exception of 1 patient with lung cancer.

Attempts have been made to correlate the severity of radiation reaction in the

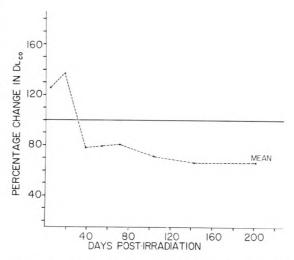


Fig. 9. In experimental studies with dogs, unilateral lung irradiation resulted in a reduction in diffusing capacity as compared to the function in the non-irradiated "control" lung. The values become greater or lesser than 100 as the function of the irradiated lung increases or decreases relative to the function of the "control" lung. The initial increase in diffusing capacity has not been explained.

lung to time-dose relationships, volume of tissue irradiated, and many other factors. In a recent paper, a relationship was described between the volume-dose of radiation to the chest and changes in diffusing capacity.1 Others have previously stated that the severity of reaction was directly related to the volume of tissue irradiated as well as the total dose.<sup>8,4</sup> It is our opinion that it is more difficult to detect radiation damage in small volumes of lung, particularly with physiologic studies, but that tissue damage occurs. We are impressed by the individual variability in response to similar doses of radiation to similar volumes of lung tissue in both the clinical and the experimental studies. The doses delivered in this clinical study were conservative and yet mild to moderate reactions developed in half of the patients. Most of them did not develop severe pulmonary insufficiency because the reserve capacity of the remaining lung was more than adequate to make up for the deficit.

One must accept some degree of pulmonary damage when delivering radiation to the chest in an attempt to palliate or eradicate most malignant conditions. In this series, the pulmonary function studies

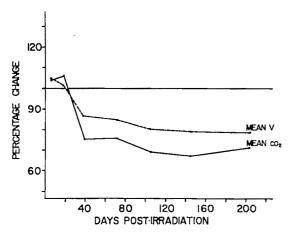


Fig. 10. The amount of carbon dioxide expired from each lung indicates the ratio of pulmonary blood flow to the two lungs. Blood flow to the irradiated lung decreases simultaneously as the ventilation diminishes. (The data presented in Figures 9 and 10 are mean changes from 4 experimental animals.)

did not particularly help to determine which patients would develop radiation reactions, but one should be more cautious about delivering high doses to the lungs when there is a reduction in pulmonary reserve. In all situations one should limit the volume of thoracic irradiation to the minimum consistent with adequate coverage of the target area.

#### CONCLUSIONS

- 1. Therapeutic doses of radiation cause injury to pulmonary tissues as evidenced by roentgenographic and physiologic studies. Two patients in this series developed serious impairment in function, but in each case there were complications associated with the malignant disease.
- 2. The adverse changes were evident within 6 months and showed little progression after 12 months.
- 3. Physiologic studies did not prove to be as sensitive as roentgenographic examination in detecting radiation damage in the lung.
- 4. The beneficial effects of radiation on lung cancer frequently outweigh the adverse effects on lung tissues, resulting in a net improvement in function.

George Cooper, Jr., M.D. University of Tennessee College of Medicine Memphis, Tennessee 38103

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## RADIOTHERAPY FOR RENAL ADENOCARCINOMA\*

By P. T. HUDGINS, M.D., and V. P. COLLINS, M.D. HOUSTON, TEXAS

THE prognosis in adenocarcinoma of the kidney (hypernephroma) can be favorably influenced by radiotherapy if advantage is taken of the characteristic features of the disease and if the patient's condition is evaluated in terms of likely benefits to be derived from treatment. Tumor factors to be considered are the growth rate, the presence of metastases and the extent of local infiltration. Patient factors to be considered are the individual's tolerance for surgery or radiotherapy which entails an assessment of the hematologic and nutritional status, the patient's age and the function of the uninvolved kidney.

Since the peak incidence of discovery of the disease is in the fifth and sixth decades of life, a considerable range in growth rate for individual tumors from rapid to very slow is observed. This does not imply that age influences growth rate but merely that slowly growing tumors must be present for a long time before they are large enough to be detected. Tumor doubling times from measurements of metastatic pulmonary deposits have varied from 26 to 158 days in a group of 7 patients studied with pulmonary metastases. Thus, prognosis even if treatment is not effective may be favorable if growth rate is slow. Bratherton<sup>2</sup> cites a case of a slowly growing untreated pulmonary metastasis observed for a period of 8 years and finally death at the age of 94 years in a man with primary adenocarcinoma of the kidney, surgically removed at the age of 79 years. The success of any form of treatment in a clinical series will be influenced by the proportion of such inherently favorable cases, and in some instances of apparent cure the absence of evident metastases may be due to the fact that metastatic deposits have not had sufficient time to reach the proportions which would allow their detection. Thus it becomes apparent that in such instances even no treatment at all is to be preferred over a vigorous assault on the tumor which will incidentally devastate a relatively compatible host.

Cohesiveness of tumor cells is another factor which influences the clinical course of the disease. Some tumors metastasize early in the development of the primary lesion, as evidenced by secondary tumors as large or even larger than the primary. In such instances, we may have to assume a more rapid growth rate in the metastasis as well as early fragmentation of cells from the primary. Metastases are also found before the primary lesion is discovered because the local growth is frequently silent, while a metastasis to bone, lung or central nervous system will produce symptoms which lead to its detection (Table 1). In 9 patients, of 36 referred to the department of radiotherapy at Baylor University College of Medicine for treatment, metastases were noted before the discovery of the primary

Table I
SITE OF METASTASES EVIDENT BEFORE
DISCOVERY OF PRIMARY LESION

Lung	1		
Bone	5	humerus femur	1 3
Brain	I	vertebra	I
Lymph Node	2	mediastinal supraclavicu	!ar

<sup>\*</sup> Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28-October

From the Department of Radiology, Baylor University College of Medicine, Houston, Texas.

lesion. Cohesiveness is not necessarily related to growth rate, but the more rapidly growing cancer will most surely reveal the presence of any metastases since these, too, will be rapidly growing. The preponderant migration of the cells of adenocarcinoma of the kidney is by the blood stream with metastases generally occurring in lung, bone and to a lesser extent in brain. Lymphatic spread to para-aortic lymph nodes, while occurring occasionally, is not usually a clinical problem since it is overshadowed by blood borne metastases to more vital structures.

Infiltration is the third characteristic of the cancer which influences the prognosis and the approach to therapy. Generally, these carcinomas are slow to invade locally and tend to have pushing borders which allow for expansion of the renal capsule with relatively late local invasion. Thus, surgical removal of the intact specimen is facilitated, even when invasion of diaphragm, bowel or spleen has occurred. Distinct surgical margins can be recognized in the excised specimen. Extension into the vena cava and abdominal wall is a much less favorable circumstance and usually prevents surgical removal. Infiltration is not necessarily related to growth rate, but is encountered more frequently in the more rapidly growing and large tumors.

The choice of treatment should, therefore, be based upon an accurate evaluation of the following tumor factors: growth rate, appearance of metastases and local invasion. Patient factors of tolerance for surgery or radiotherapy must be weighed against the likely benefits and the complications that are to be derived from treatment. How then may such an appraisal be achieved? Unfortunately, the clinical history is not often of great value in the evaluation of the duration of the disease since, when an adenocarcinoma of the kidney has reached such proportions that it produces symptoms, it is rather late in its development, and even symptoms of short duration are frequently preceded by a long interval of slow silent growth. However, the history should not be neglected, and, if previous roentgenograms are available which show measurable tumor, the growth rate can be estimated and a fairly accurate prognosis may be given. Chest roentgenograms should be obtained and closely scrutinized in search of metastases before treatment has begun. Routine bone surveys are not necessary since the discovery of asymptomatic bone metastases is unlikely. Areas of bone pain or tenderness must be investigated thoroughly for metastases. Roentgenographic examination of the skull for evidence of intracranial metastases is of no value. Signs and symptoms of intracranial metastases require investigation by angiography, pneumoencephalography, or brain scanning.

The physical estimate of renal mass is only a rough guide to the local problem. Locally, the size is not so much of a surgical problem as is the presence of invasion. Renal angiographic studies have a degree of diagnostic accuracy for renal carcinoma which approaches that of histologic diagnosis. These studies as well as nephrotomography serve to localize the tumor accurately and to demonstrate its dimensions if radiotherapy is the method of treatment selected. Perirenal air insufflation is ancillary to these studies and will give some idea about the local infiltration and resectability. All of these special procedures are not indicated in every case and selection must be individualized. In the large tumor where resectability is in doubt, perirenal air studies may be chosen; in the small mass where cyst-tumor differential is wanted, drip infusion pyelography or renal vascular study would be chosen.8 Prior to either surgery or radiotherapy, the presence of a functioning kidney on the opposite side must be established by excretory pyelography.

The hematologic status must be investigated, and while a sporadic case will show a secondary polycythemia associated with renal adenocarcinoma, anemia is a more frequent problem and should be corrected by transfusions of packed red blood cells. The age of the patient and nutritional sta-

tus will have a decided effect upon individual tolerance to therapy.

Surgical removal is indicated whenever feasible, but, if a lesion is nonresectable because of local invasion or metastases which are rapidly growing or life threatening, radiotherapy can offer worthwhile benefits. In the presence of a solitary or slowly growing metastasis and a resectable primary tumor, removal of the primary lesion should be considered even though total eradication of the disease is not effected.

Cure of renal adenocarcinoma with radiotherapy alone is rare, but when the disease is carefully managed and full advantage taken of the natural course of the disease, satisfactory control for prolonged periods may be achieved. It must be realized that if surgery is to follow radiotherapy, it should be delayed from 4 to 6 weeks beyond completion of treatment so that the early phase of hyperemia and edema incident to therapy will not complicate the surgery.

Treatment is designed to include the known extent of the disease and is given to the predicted tolerance of the patient. The amount of radiation given is limited by the volume which must be included as well as the adjacent sensitive vital structures. The opposite kidney must be spared from all but very minimal irradiation to avoid the complication of radiation nephritis. The spinal cord is rarely of concern at the level of the kidney since only a small terminal portion is ever included in the intense radiation zone. The small bowel is a very real limiting factor and its inclusion in the heavily irradiated tumor zone can hardly be avoided. It is the structure which prevents administration of radiation doses intended to eradicate local disease. Nonetheless, as will be seen in 2 of the illustrated cases, worthwhile benefits can be expected from even limited therapy of the primary disease. Recurrences after surgical excision are similarly worthwhile treating. Postoperative radiotherapy is offered only if there is known residual disease in the tumor bed or in regional lymph nodes, since the hazards of small bowel injury hardly justify the routine prophylactic use of treatment. Such residual should be carefully outlined at the time of surgical exploration with radiopaque markers so that external beam therapy can be accurately directed. If radiogold or radon seeds are available and surgical-radiotherapeutic liaison has been established, implantation at the time of exploration offers the advantage of marking and giving partial radiation dosage without damage to adjacent sensitive structures.

Treatment to metastatic disease may be given with the expectation of preventing the occurrence of pathologic fracture, to promote healing of fracture, to relieve pain, cough, hemoptysis, or to allay a life threatening complication.

The cases which follow illustrate some of the varying features of the disease as well as the benefits which may be derived from radiotherapy.

#### CASE REPORTS

Case I. This 40 year old woman in November of 1961 experienced a painful left shoulder following an automobile collision. In January, 1962, a biopsy of the lytic lesion of the left shoulder revealed adenocarcinoma. Two weeks later a left nephrectomy was performed and adenocarcinoma of the kidney was found. A radiogold seed implant to the left shoulder supplemented by external radiotherapy resulted in recalcification of the lytic lesion involving the glenoid, and a useful shoulder joint was preserved.

Following this, the patient developed, during a 2 year interval, rib, lumbar and cervical spine metastases and a lytic lesion of the right glenoid. Each of these lesions was treated in turn, with complete relief during the ensuing 2 years. There was also recalcification of the lytic lesion in the right shoulder. Although there was continuous progression of disease, the patient remained free of pain most of the time until her death 2 years following nephrectomy.

Case II. In April of 1963, this 40 year old man (Fig. 1, A and B) developed left upper quadrant pain and abdominal fullness. In July, 1963, surgical exploration disclosed a non-resectable large adenocarcinoma of the kidney

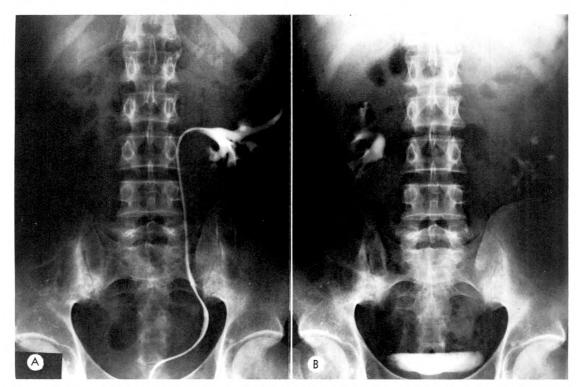


Fig. 1. Case II. (A) Retrograde pyelogram before therapy showing large left renal mass. (B) Excretory urogram following completion of therapy to left renal mass.

which involved the aorta, vena cava and retroperitoneal structures. On September 11, 1963, the patient received a total of 3,000 r tumor dose in 29 days from a 2 million volt Van de Graaff machine through 12×15 cm. opposing fields. The object of therapy was to produce shrinkage of the mass and possibly allow resection. Following completion of therapy, there was evident regression of the disease to palpation.

On October 15, 1963, surgical resection of the left renal mass was accomplished. The mass weighed 1,790 gm. A portion of infiltrated diaphragm was included in the specimen but the major vessels were free of involvement as were the renal artery and vein. Although the capsule was invaded, there was no evidence of infiltration beyond the margin of resection.

This patient is living and well.

CASE III. This 69 year old man (Fig. 2, A-E) in July, 1962 experienced a single episode of hematuria. He had been on anticoagulant therapy for suspected coronary occlusion. The anticoagulants were discontinued and no further investigation was done. In January, 1963,

he developed a cough following an episode of influenza, which persisted.

In June, 1963, multiple pulmonary and scalp metastases were discovered and, subsequently, perirenal air roentgenograms demonstrated a

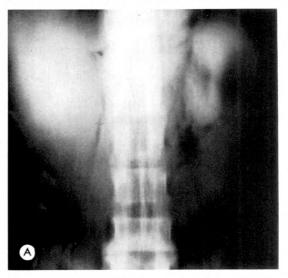


Fig. 2. Case III. (A) Right retrograde laminagram with presacral injection of O<sub>2</sub> showing large right renal mass before therapy.

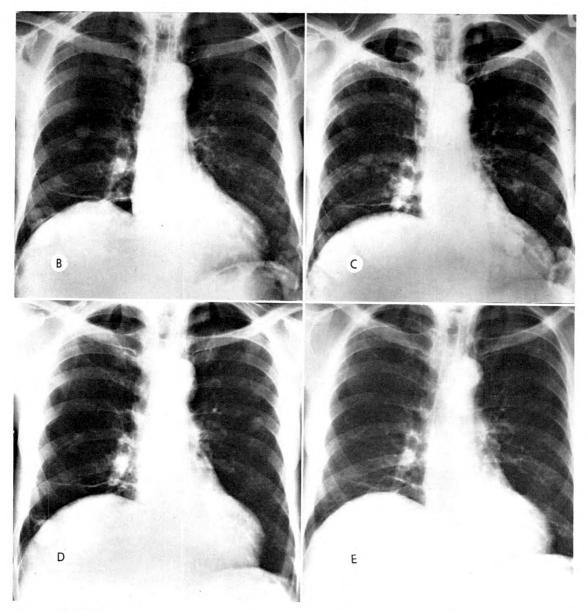


Fig. 2. (B) Multiple pulmonary metastases prior to therapy. (C) Further growth of pulmonary metastases near completion of therapy. (D) Evident regression on 3 month follow-up. (E) Eleven months following therapy. Complete regression of all pulmonary nodules.

large right renal mass with liver and diaphragmatic invasion. A review of previous chest roentgenograms showed that growth of the pulmonary nodules had been rapid. The patient was anxious to return to his home out of the city so a rapid course of radiotherapy, consisting of 2,500 r delivered through 12×12 cm. opposing fields to the large renal mass during a

period of 14 days, was administered.

In November, 1963, there was evident regression of the abdominal mass and pulmonary metastases. The pulmonary metastases had not been treated. In May, 1964, there were no detectable pulmonary metastases, and the patient was symptom free.

In September, 1964, regrowth of the renal

mass was evident. In October, 1964, multiple small pulmonary nodules were again observed. The patient expired in December, 1964 from rapid progression of the disease.

A number of cases has been reported in the literature of spontaneous regression of metastases from adenocarcinoma of the kidney following surgical removal of the primary lesion. <sup>6,7,9</sup> Such cases, although rare, make attempts to resect or irradiate the primary tumor worthwhile even in the presence of distant metastases.

In conclusion, it should be realized that 3 factors, rate of growth, presence of metastases, and local invasion play the dominant role in determining the status of the carcinoma. When properly evaluated, and therapy planned in accordance, prolonged control and remission can be achieved in many patients.

P. T. Hudgins, M.D. Department of Radiology Baylor University College of Medicine Houston, Texas

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## BILATERAL WILMS' TUMOR, INCLUDING REPORT OF A PATIENT SURVIVING TEN YEARS AFTER TREATMENT\*

By JUSTIN J. STEIN, M.D.,† and WILLARD E. GOODWIN, M.D.,‡ LOS ANGELES, CALIFORNIA

THERE is considerable confusion in the literature regarding the proper name for Wilms' tumors, the great majority of which occur in infants and children. Some of the most commonly used names are embryonal adenomyosarcoma, nephroblastoma, embryoma of the kidney, and carcinosarcoma. The most popular and readily recognized name is "Wilms' tumor."

#### AGE, SEX, AND INCIDENCE

About 90 per cent of Wilms' tumors develop before the age of 6 and the average age is approximately 3 years. When Abeshouse¹ reviewed 856 cases reported by 81 surgeons, he found that the average age was 3.2 years and that both sexes and either kidney may be equally affected. Snyder, et al.⁴¹ found that a total of 108 cases of Wilms' tumors had been reported in adults. The oldest patient was 80 years of age.

Wilms' tumor is the second most common malignant abdominal tumor found in infants and children. The majority of masses found in the abdomen in this age group are either Wilms' tumor or neuroblastoma.<sup>17</sup> Dargeon,<sup>10</sup> in a study of 1,418 malignant tumors diagnosed in infants and children at the Memorial Hospital Center from 1926 to 1956, noted that there were 93 Wilms' tumors and 171 neuroblastomas in the group.

The incidence of Wilms' tumor at the Mayo Clinic from 1941 through 1955 was I per 20,000 admissions. Twenty-four patients with such tumors were diagnosed in 78,961 admissions from 1925 to 1949 at the James Whitcomb Riley Hospital for Children in Indianapolis. Only 8 of the children

with Wilms' tumor were over 3 years of age.18

At the Children's Hospital of Philadelphia, approximately 30 to 35 per cent of all the cancers in children are leukemia and lymphomas; 25 to 30 per cent involve the brain, spinal cord, and the eye; 20 per cent are listed as tumors of the flank, primarily Wilms' tumor and neuroblastoma; and the remaining 20 per cent are miscellaneous types of tumors.<sup>17</sup>

Klapproth<sup>20</sup> reported 45 cases seen at the Cleveland Clinic during the years 1921 to 1957. Snyder et al.<sup>41</sup> state, "Wilms' tumors comprise an average of 1:2,000-3,000 admissions of pediatric hospitals." Stowens<sup>42</sup> believes that this type of tumor accounts for approximately 20 per cent of all solid tumors diagnosed in patients less than 12 years of age. Statistics vary considerably between different reporting hospitals, depending upon local and special circumstances.

Pearson and associates<sup>33</sup> reported that 96 children with Wilms' tumors were treated at the Christie Hospital and Holt Radium Institute between 1940 and 1960. Since 1949, an average of 6 cases per year have been referred for treatment to that hospital. Between 1953 and 1961, 811 cases of malignant disease in childhood were registered in the Manchester Children's Tumor Registry; 44 of these were Wilms' tumors.<sup>33</sup>

#### BILATERAL INVOLVEMENT

Abeshouse<sup>1</sup> found that 1.4 per cent of the reported cases of Wilms' tumors were bilateral. Creevy and Reiser<sup>8</sup> reported that 2.4

<sup>\*</sup> Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October 1, 1066.

From the Departments of Radiology (Radiation Therapy Division)† and Surgery (Urology),‡ University of California, Center for the Health Sciences, Los Angeles, California.

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per cent of 1,170 cases were bilateral. Four per cent of the 95 cases at the Los Angeles Children's Hospital were bilateral. 41 Martin and Kloecker<sup>28</sup> believe the incidence of bilateral tumors to be from 5 to 10 per cent. They reported 3 cases of bilateral involvement in 30 patients. The tumors were thought to be unilateral before operation. Two of 12 cases diagnosed at the UCLA Center for the Health Sciences between 1955 and 1962 were bilateral. In 1962, Snyder et al.41 stated that 50 cases of bilateral Wilms' tumors had been reported in the literature and that most of the cases were diagnosed at autopsy. Four per cent of the 96 cases at the Christie Hospital and Holt Radium Institute were bilateral.88 Five or 5.6 per cent of 89 children with pathologically confirmed Wilms' tumors, first diagnosed between 1942 and 1957, and reported to the California Tumor Registry had bilateral involvement.26

Scott<sup>39,40</sup> is of the opinion that metastases to the opposite kidney may account for some of the cases of bilateral Wilms' tumors. He noted that of a total of 234 cases reported between 1914 and 1953, only 2.8 per cent were bilateral. He believes that if a tumor of one kidney is promptly found and treated, there is less opportunity for metastasis to the other kidney.

It is quite possible that a much higher incidence of bilateral involvement would be found than is now reported if, at the time of the surgical exploration, both kidneys were examined. This should be done in spite of normal excretory urograms and the absence of symptoms related to the "normal" kidney.

#### SYMPTOMS

The most common findings or symptoms with Wilms' tumors are (1) abdominal mass, (2) pain, (3) fever, and (4) hematuria. Weakness and general malaise may also be present, especially when the tumors are large. In adults with hypernephromas, the most common signs and symptoms are (1) hematuria, (2) pain, and (3) abdominal mass which is the reverse order from that

reported for infants and children with Wilms' tumors.

#### DIAGNOSIS

Most Wilms' tumors can be diagnosed on the basis of age, the presence of a palpable abdominal mass, and the findings on intravenous urography. Only in a few cases it is necessary to resort to retrograde pyelography. When retrograde pyelography is done, precautions must be taken in order that undue trauma or penetration through the kidney does not occur.

Calcification may be noted in the tumor because of calcified old necrotic areas, but this is not common. The kidney may be displaced and have an abnormal renal contour. Distortion of the renal pelvis and calyces may occur. Obstruction at the ureteropelvic junction may produce pyelectasis of varying degrees. For definitive diagnosis, surgical exploration is necessary.

Prout and Macalalag<sup>36</sup> have reported that the urinary lactic dehydrogenase (LDH) is elevated when kidney tumors are present. After the tumors are removed, the urinary level of the enzyme returns to normal. They studied 4 children with Wilms' tumor and found the urinary LDH to be elevated.

Neuroblastoma, retroperitoneal teratoma, polycystic kidney, hydronephrosis, and solitary renal cyst are the most common lesions which should be considered in the differential diagnosis.

Melicow and Uson<sup>29</sup> studied the findings in 653 patients with palpable abdominal masses. There were 281 children in this group who had lesions treated surgically. Approximately one-third of the genitourinary tract lesions (which accounted for one-half of this group of 281 patients) had Wilms' tumors or adrenocortical neoplasms. The genitourinary tract lesions included hypernephromas in 56 patients, cystic disease of the kidney in 31, and Wilms' tumor in 42. Ten patients had miscellaneous types of lesions.

Roentgenographic examination of the chest should always be done. Too much

manipulation or palpation of the abdominal mass should be avoided. If a neuroblastoma involving the kidney is suspected, a bone survey should be done in addition to the other recommended procedures. Metastases to bone from Wilms' tumors are infrequent.

Koop et al.<sup>22</sup> believe that the vanilmandelic acid (VMA) levels in the urine should be determined in any child with unexplained diarrhea of a chronic nature, since patients with neuroblastoma and other neurogenic tumors secrete this acid in their urine as an end-product of norepinephrine metabolism.

#### TREATMENT AND PROGNOSIS

There is considerable controversy as to the best method of management of the patient with operable Wilms' tumor. There are many advocates for preoperative irradiation followed by nephrectomy and post-operative irradiation. Others urge immediate nephrectomy followed by postoperative irradiation. Some prefer preoperative irradiation followed by nephrectomy. Radiation therapy is not recommended as the only method of treatment for an operable Wilms' tumor. Surgery without any other type of therapy is rarely recommended.

Because so few cases are available for study in any one institution, it is difficult to obtain experience with a large series of patients treated by different techniques in the same institution.

Kinzel et al.<sup>19</sup> report that in their experience the most effective treatment consists of preoperative irradiation, nephrectomy, and postoperative irradiation. With this treatment regimen, a 3 year survival rate of 57 per cent was obtained as compared with 23 per cent for those patients who had only postnephrectomy radiation therapy.

Preoperative radiation therapy has been advocated, especially for large tumors, in order to reduce the size to facilitate removal of the tumor with less manipulation and trauma. Also, preoperative radiation therapy causes the destruction of many tumor cells. Since the transabdominal approach to the surgical removal of Wilms' tumors has been used with prompt isolation and

ligation of the renal vessels, large tumors can be removed without undue mechanical problems.

Koop et al.22 recommend nephrectomy, actinomycin D for 5 days, and postoperative irradiation when the tumors are small, diagnosis is made early, and no metastases are present. If pulmonary metastases are present at the time the initial diagnosis is made, the same type of treatment is done. The radiation dose to the kidney area is 2,000-2,500 r (tissue dose) and 1,200 r (tissue dose) to the lung fields. Actinomycin D is repeated in 5 day courses (15  $\mu$ g./kg.) every 6 weeks for 6 months, and every 3 months for 6 to 9 months. They have reported 2 patients with bilateral nephroblastoma alive and well 2 years and 2 months, and I year and I month following the administration of actinomycin D and radiation therapy. Surgical removal of the tumors was not done.

The treatment program at the Christie Hospital and Holt Radium Institute is to treat all patients with Wilms' tumors regardless of the stage of the disease.<sup>33</sup> For the small primary tumors, nephrectomy followed by postoperative irradiation is done; for large primary tumors, preoperative irradiation is given, followed by nephrectomy in 4 to 6 weeks after the end of treatment. Parallel opposed fields with a tumor dose of 2,500 r in 5 to 6 weeks are given preoperatively or postoperatively, as indicated. The tumor dose to the opposite kidney never exceeds 2,000 rads. An overall survival rate of 30 per cent for the 96 cases was obtained.

Harper and Anderson<sup>16</sup> described a 10 month old white male with bilateral Wilms' tumor. The upper, middle, and lower poles of the right kidney and the upper and lower poles of the left kidney were involved. The patient received a tumor dose of 2,620 r delivered in 35 days to both kidneys (conventional roentgen-ray therapy). Excellent result was obtained. The patient was readmitted 5 months later because it was thought that the left kidney was palpable. A total of 75  $\mu$ g./kg. of actinomycin D was given in 4 days. Also, 1,4 $\infty$  r tumor dose was delivered to the left kidney region us-

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ing cesium 137 therapy. The patient has remained well.

Probably the most popular method of therapy at the present time is nephrectomy followed by radiation therapy. A total tumor dose of approximately 3,000 r is given in 3 to 4 weeks, using anterior and posterior fields. Gross<sup>15</sup> reported a cure rate of 47.3 per cent for the period 1940 to 1947 for patients treated by emergency surgery and immediate postoperative radiation therapy.

Neuhauser et al. 31 reported on the effects of roentgen therapy to the growing spine in children who were irradiated because of retroperitoneal or paravertebral neoplasms. Thirty-four children were observed for periods of from 2 years and 2 months to 13 years and 3 months after treatment. Their conclusions were that 1,000 tissue r failed to produce permanent deformity of the vertebrae; minor disturbances occurred from doses between 1,000 and 2,000 r delivered to the spine, but dosages in excess of 2,000 tissue r would probably cause definite growth disturbances. If the portion of the spine which is irradiated receives uniform irradiation, scoliosis can be avoided. Conventional roentgen-ray therapy or megavoltage radiation therapy is utilized. The use of cobalt 60 or other megavoltage equipment may be desired because little, if any, skin reaction is produced, thereby ensuring greater comfort for the infant or child. It is doubtful that any appreciable difference will be noted in the over-all end results, regardless of which type of equipment is used.

Klapproth<sup>20</sup> analyzed the results of treatment in cases reported in the world literature between 1940 and 1958. He is of the opinion that there is no statistical evidence for a significant difference in the treatment results among the three prevailing methods of therapy which are as follows: preoperative irradiation and nephrectomy with a cure rate of 27.2 per cent in 103 patients; nephrectomy and postoperative irradiation, with a cure rate of 26.2 per cent in 423 patients; and nephrectomy with preoperative and postoperative irradiation with a cure rate of 24.1 per cent in 145 patients. He states that, since the re-

sults of nephrectomy alone are poorer than those from combinations of surgery and radiotherapy, radiation therapy should be used in every patient who is operated upon who has a chance for potential cure.

Successful nephrectomies for infants with Wilms' tumors have been performed on an infant 12 hours of age, 1 infant 3 days old, and 1 aged 4 days at the Los Angeles Children's Hospital.41

D'Angio et al.<sup>9</sup> have reported favorable responses in patients with Wilms' tumor who have had combined roentgen irradiation and the intravenous administration of actinomycin D. Altman<sup>3</sup> found that actinomycin D has a definite antineoplastic effect on patients who have metastatic disease from Wilms' tumor. A potentiation of the effect has been described when this chemotherapeutic agent is used with radiation therapy.

Although D'Angio et al.<sup>9</sup> are enthusiastic about the use of actinomycin D combined with radiation therapy in the treatment of Wilms' tumor, Kligerman<sup>11</sup> states that "Taking all accounts in hand of the tumor responses and side effects of actinomycin D, it would seem that the case for therapeutic synergism has not yet been made."

Lattimer et al.<sup>24</sup> found age at the time of nephrectomy to be a most important factor in determining prognosis. The results of 36 children treated by nephrectomy alone or with radiation was as follows: 73.3 per cent of those less than 2 years of age and also 90 per cent of those operated upon before the age of 1 year survived for at least 3 years. Only 18.5 per cent of children aged 2 years and older lived for 3 or more years. They noted that only 2 of 25 patients treated between 1895 and 1934 were considered to be cured. These results are in sharp contrast to the more favorable results now obtained.

Bjelke<sup>3</sup> reported a survival rate of 30 per cent for 2.5 years for children less than 2 years of age at the time of diagnosis and 14 per cent for those aged 2 to 5 years.

Kinzel et al. 19 reported that 9 of 15 patients (67 per cent) under 2 years of age, but only 4 of 32 patients (13 per cent) 2 years of age or older survived 5 or more years.

At the Los Angeles Children's Hospital, 22 or 23.1 per cent of the 95 cases have survived more than 2 years since treatment and 14 or 14.7 per cent have survived over 5 years. <sup>41</sup> This report lends support to the importance of age at the time of the initial definitive treatment since 9 or 64 per cent of the 14 patients were under 2 years of age at the time of treatment.

Vaeth and Levitt<sup>48</sup> reported the end results of treatment of 30 patients with histologically verified Wilms' tumors. Thirteen or 76.4 per cent of 17 patients less than 2 years of age survived 5 years. Only 6 of 16 patients with invasion of the capsule survived for 5 years. They described a 5 year survival rate of 53.5 per cent for patients who had preoperative irradiation, nephrectomy, and postoperative irradiation. The preoperative irradiation consisted of 2,500 r in 3 to 4 weeks, delivered to the mid-plane and followed in 3 to 4 weeks by transperitoneal nephrectomy. Two weeks after nephrectomy, postoperative irradiation was begun and a total dose of 3,000 r was given in 4 weeks. Chilko reported 2 children with inoperable Wilms' tumor who were treated by roentgen-ray therapy and who are well more than 20 years. Their diseased kidney was removed 10 years after treatment.

Patients may live for many years and then succumb to metastasis. If a patient survives for 2 years without recurrent disease, there is a good chance that the patient may be cured. Campbell<sup>4</sup> reports a patient who had a Wilms' tumor removed at the age of 4 years only to have a small nodule appear in the scalp followed by metastases to the lungs, liver, bones, retroperitoneal lymph nodes, and adrenals, and thrombosis of the vena cava, causing death at the age of 29 years.

Goldberg and Diaz<sup>14</sup> reported a patient 21 months of age with bilateral Wilms' tumor involving the lower pole of both kidneys. The patient was explored and a biopsy was made of the right kidney tumor. The patient then received radiation therapy to both kidneys, followed by resection of the lower poles of the kidneys several weeks apart. The patient was alive and well

3 years after the original diagnosis.

Close et al.<sup>6</sup> in 1956 reported an 8 month old boy who was first seen on January 27, 1952, with bilateral upper abdominal masses and gross hematuria. A right nephrectomy was done and roentgen-ray therapy was given to the left kidney tumor. A partial resection of the left kidney was done. A total tumor dose of 1,600 r was given to the right kidney region postoperatively and the total tumor dose to the left kidney area preoperatively and postoperatively was 2,300 r. This boy remained alive and well over 12 years with the last follow-up examination in July, 1964.<sup>34</sup>

In 1953, Gross<sup>15</sup> reported a patient with bilateral Wilms' tumor who had survived for 12 years without recurrence. The treatment consisted of right nephrectomy and radiation therapy to the right kidney region and to the left kidney. Rickham<sup>87</sup> reported a case of bilateral Wilms' tumor in which a left nephrectomy was done along with a partial nephrectomy of the right kidney. Postoperative radiation therapy was given (2,800 r to the right kidney) but with a total tumor dose of only 2,000 r to the remaining kidney tissue. Pearson et al.<sup>88</sup> report that this patient has remained well for 8 years.

#### TREATMENT OF METASTATIC LESIONS

Kiesewetter and Mason<sup>18</sup> reported a female patient less than I year of age who had surgery for a Wilms' tumor. The patient developed cerebellar metastases which were removed a year after the first operation. This patient was alive and well at the Io year follow-up.

At the Los Angeles Children's Hospital, 4 of 5 patients were alive and free of metastases 17, 19, 36, and 59 months, respectively, after resection of a pulmonary metastatic lesion.

Five patients at the Christie Hospital and Holt Radium Institute have survived several years after radiation therapy of the whole chest. One of the patients developed cor pulmonale due to radiation fibrosis of the lungs and died 18 years later and 2 of the patients are alive and well over 10 years

after the treatment of chest metastases. A 3 year survival rate of 14 per cent of 35 patients treated for pulmonary metastases by the whole chest irradiation technique was reported  $(2,5\infty)$  rads in 5 to 6 weeks to the entire chest).<sup>33</sup>

Murphy<sup>80</sup> has not obtained permanent control of pulmonary or brain metastases from Wilms' tumors by radiation therapy. He has stated that "a persistent or recurrent neoplasm in the abdominal region can often be clinically eradicated by intensive irradiation."

#### RADIATION NEPHRITIS

The possibility of radiation nephritis must always be kept in mind when patients with large abdominal tumors are irradiated. Campbell<sup>4</sup> reported a 2 year old patient with Wilms' tumor who died of acute radiation nephritis and, also, another patient with a Wilms' tumor who has survived 15 years postoperatively, but requires 3 to 4 transfusions each year because of radiation nephritis in the opposite kidney.

Sagerman<sup>88</sup> reported a case of radiation nephritis in a 4 year old boy who received an estimated tissue dose of 2,370 r of absorbed radiation in 42 days. The radiation therapy was combined with actinomycin D.

Doub et al., 12 in 1926, described the production of radiation nephritis in dogs and in the following year reported 2 cases of hypertensive nephritis following the irradiation of malignant tumors. Kunkler is of the opinion that a tumor dose of approximately 2,300 rads to the whole of both kidneys in a period of 5 weeks or less carries the risk of initiating radiation nephritis. Luxton that a found that the symptoms of acute radiation nephritis do not appear until a few months after the radiation therapy has begun. He describes the latent period in adults as from 6 to 13 months and a shorter latent period in children.

In 1948, the technique of roentgen-ray treatment for seminoma at the Christie Hospital and Radium Institute, Manchester, England, was varied so that both kidneys were included in the radiotherapy field. Previously, only limited volumes of

both kidneys were included. With the change in technique, both kidneys received at least 2,300 r during a period of 5 weeks.

Paterson<sup>32</sup> found, as a result of his experience in the treatment of seminoma of the testis when the irradiated volume included the whole of both kidneys in such a way that the kidneys received a dose of 2,500 r or over in 3 weeks, that damage resulted and the cure rates were decreased. He commented that "whatever happens, some part of at least one kidney must be preserved free of radiation, or if the extent of involvement is such that this is impossible the total dose must not exceed 2,000 r."

The possibility of radiation nephritis must be kept in mind in treating these patients as well as when large abdominal tumors are irradiated and the kidneys are included in the field.

Malignant hypertension caused by radiation therapy and involving only one kidney may be relieved by nephrectomy. Levitt and Oram<sup>25</sup> reported a patient who received 3,000 r to the left kidney and 2,000 r to the right kidney in the postoperative radiation therapy of a patient with metastases from a seminoma. Eleven years later he developed malignant hypertension which was cured by a left nephrectomy. Dean and Abels<sup>11</sup> described the occurrence of hypertension in a patient 7 years after she received 4,600 r in 25 days to the left kidney region. The blood pressure returned to normal after nephrectomy.

#### CRITERIA FOR SURVIVAL

Collins' has postulated that following the time of diagnosis of a patient with Wilms' tumor, the patient would be at a risk of recurrence of tumor for a period equal to his age at the time of diagnosis plus 9 months. In other words, the growth of a Wilms' tumor would be calculated at 9 months for the period from conception to birth, then the period of silent growth from birth to diagnosis, and a period of risk equal to the period of silent growth. If the child was 2 years of age at the time of diagnosis, the period of silent growth would be 2 years plus 9 months. If the child survived an

additional 2 years and 9 months, it would be beyond the risk of recurrence or cured.

Platt and Linden<sup>86</sup> believe that Collins' hypothesis as applied to Wilms' tumors represents a clinically useful appraisal. They also believe that the 2 year fixed interval rate is an equally effective means for the estimation of prognosis for patients with Wilms' tumor.

#### REPORT OF A CASE

LONG TERM SURVIVAL FOLLOWING TREATMENT FOR BILATERAL WILMS' TUMOR

A 4 year old white male (S.H.) was first seen on September 26, 1955, with the chief complaint of blood in the urine of approximately 36 hours' duration. The patient was free of symptoms until approximately 36 hours before being seen by Dr. David N. Grey, a urologist. It was noted by the patient's parents that he passed gross blood in the urine without pain. The urine was never free of blood from the onset. The patient had no chills or fever associated with this and no urinary symptoms other than frequency.

His weight was 35½ pounds and had been so for the preceding 6 months. The patient had always been a thin boy and the parents and the referring physician were not concerned by his failure to gain weight during this 6 month period. He had grown considerably in height. He had had no cough or chest pain during the previous 6 months, and his bowel movements, except for the past few days when he had been constipated, had been normal. There was no history of bed wetting and no unexplained fever in the past.

The patient was born of a normal pregnancy at full-term, weighing 8 pounds, 14 ounces. Growth and development had been entirely normal. He had a concussion at the age of 6 months; skull roentgenograms were negative. At the age of 1½ years, he was bitten by a black widow spider. There were no childhood diseases and no previous surgery.

The patient's mother was 30 years of age, living and well. His father was 32 years old and in excellent health. The patient was the only child. There was no family history of tuberculosis, diabetes, kidney or heart trouble.

His physical examination was negative except for the abdomen and genitourinary system. His blood pressure was 90 systolic and 60

diastolic, pulse 90, and respiration 24. He was a pale, thin, alert, intelligent cooperative male.

Abdominal examination showed no scars or herniae. On inspection of the abdomen, there was a slight prominence in the right flank. The left kidney was not enlarged or tender to palpation. In the region of the right flank, a large mass could be felt which extended almost to the iliac crest. It was very firm, nontender and moderately mobile. No other organs or masses could be palpated. The external genitalia were negative. The impression was a mass of the right kidney, probably Wilms' tumor. It was recommended that intravenous pyelography be performed immediately and the patient admitted to the hospital for surgery within 24 hours, provided the roentgen examination confirmed the clinical impression.

The intravenous pyelograms were diagnostic of a right renal tumor. The left kidney appeared to be normal. Chest studies were negative.

Right nephrectomy was performed by Dr. Grey on the same day that the pyelographic examination was made. At surgery, it was noted that the tumor occupied the lower two-thirds of the right kidney and was adherent to the vena cava in its lower portion; the capsule of the tumor was inadvertently punctured. The operative area was thoroughly irrigated and postoperative radiation therapy was recommended.

On September 27, 1955, the patient was started on postoperative irradiation, the series being completed on October 4, 1955. A tumor dose of 3,049 rads was given in 5 weeks using conventional roentgen-ray and cobalt 60 radiation therapy equipment.

The patient did well until March, 1956. He was re-admitted to the hospital on March 21, 1956, with the chief complaints of anorexia, vomiting, and listlessness of I week's duration.

Physical examination revealed a large firm smooth mass in the left-upper quadrant which filled the flank and extended almost to the crest of the ilium; it was moderately tender. The spleen and liver were not enlarged. His hemoglobin was 9.6 gm.; the white blood cell count 9,150 with 80 per cent polymorphonucleocytes.

He did not void all day on March 22. Intravenous pyelograms showed no contrast medium in the region of the mass in the left kidney. Chest roentgenograms and bone survey were negative for metastases. Thirty red blood cells and 5 to 10 white blood cells per high power

field were noted on analysis of the urine.

Cystoscopic examination on March 23, revealed only a few cubic centimeters of urine in the bladder. He was given a transfusion of I unit of whole blood.

On March 24, a urologic staff conference was held and it was decided that a needle be inserted into the lesion for evidence, if any, of fluid to rule out hydronephrosis. This was done and no fluid was obtained. The patient left the hospital on April 1, 1956.

On May 16, 1956, the patient was readmitted. He was generally listless, but ambulatory, mildly active, and had a fairly good appetite. The history showed moderate weight loss, pain, and the presence of a large left abdominal mass.

On May 18, 1956, an exploratory operation was performed through a left abdominal flank exposure. The only normal kidney tissue was noted in the upper pole area. The tumor was outlined by silver clips over a continuous wire suture. No biopsy was taken but the pathologist was present in the operating room and concurred in the diagnosis of Wilms' tumor. The radiation therapist was also present.

The patient was started on cobalt 60 therapy on May 28, 1956 and the series was completed on June 29, 1956. A total tumor dose of 3,524 rads was given in 32 days to the tumor area through an anterior and posterior field. There was a rapid improvement during treatment. Every effort was made to shield the small amount of remaining normal kidney tissue.

The last follow-up examination on this boy was September 11, 1965, approximately 10 years after treatment of the original primary Wilms' tumor and 9 years and 3½ months after radiation therapy for the second primary Wilms' tumor. The possibility of this second lesion being metastatic was considered but this was not thought to be likely. Had the supposedly "normal" kidney been explored at the original operation, it is conceivable that this second tumor would have been discovered.

He was in excellent health on September 11, 1965, growing normally, and had no complaints. The blood pressure was 126 systolic and 70 diastolic. Urinalysis and complete blood cell count were normal. The blood creatinine was 1.3 mg. per cent. The chest roentgenogram was negative for metastasis. The intravenous pyelograms revealed slight dilatation of the upper collecting system but no evidence of recurrent tumor.

#### COMMENT

This case is certainly illustrative of the fact that one cannot tell how effective radiation therapy will be until it is tried. Also, that one should not give up hope wherever there is any possibility of either cure or of effective palliation. This same treatment technique was tried about the same time on a 52 year old man who had been born with one kidney and who developed a hypernephroma of that kidney with hematuria. He obtained a good temporary palliative result.

#### SUMMARY

Excellent palliation and even cure are possible in some patients with Wilms' tumors even though both kidneys may be involved.

If the patients survive more than 2 years after termination of therapy without recurrence or persistence of disease, the chances for permanent cure are excellent.

The incidence of involvement of both kidneys may be as high as 5 to 10 per cent. The supposedly "normal" kidney should be examined at the time of surgery in spite of normal diagnostic studies in order to rule out bilateral involvement.

When patients with bilateral Wilms' tumors are treated, the possibility of producing radiation nephritis must be kept in mind.

Justin J. Stein, M.D. Department of Radiology UCLA Center for the Health Sciences Los Angeles, California 90024

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# THE COMBINED TREATMENT OF CARCINOMA OF THE RECTUM WITH COBALT AND CHEMOTHERAPY\*

By ESMOND MILLINGTON, F.R.C.S., F.F.R. sussex, england

THE radical treatment of tumors of the gastrointestinal tract falls squarely within the province of the surgeon because of their radioresistance and the difficulties of radiotherapeutic access and uniform irradiation. These factors, first pointed out by Regaud in 1929, are still significant in 1965, in spite of our technical advances. The surgeon, is, however, not always able to deal with the problems of anatomy and physiology involved in complete removal, and some patients are not fit for surgery of any kind. Radiotherapists are, therefore, asked to assist in treating patients with these tumors, either ab initio when surgery is impossible for local or general disease, or when recurrent or residual disease is present after operation. Thus there is a fair amount of information available about the response in these cases and from time to time surprisingly good results have been reported such as those from Wang and Schultz.8 Murdock and Kramer have commented on the waves of interest shown by radiotherapists in carcinoma of the rectum and colon, peaks being shown between 1925 and 1930 and again between 1935 and 1940. After these there was a profound depression until some 10 years ago when the general use of supervoltage equipment and the availability of cytotoxic drugs revived interest. Today most Radiotherapy Departments are accepting cases more readily, especially when the anorectal region is involved.

When radical radiotherapy has been attempted, most reports indicate a 5 year survival rate of 10 per cent or less, with a considerable toll in the surviving cases of fibrosis and other pelvic sequelae. The results of surgery appear to be static, and

informed opinion suggests that there is unlikely to be any improvement in the future. The results of patients treated in St. Mark's Hospital include over 2,000 surviving operation between 1928 and 1952,3 of whom 98.5 per cent were traced, and these show an over-all survival rate of just over 50 per cent after 10 years, with an operability rate exceeding 90 per cent. The variation of survival time with spread of the disease follows the pattern seen in other sites varying from 95 per cent in Duke's "A" Group confined to the rectum itself, 75 per cent in "B" Group with perirectal spread to 25 per cent in "C" Group with lymphatic spread. The question as to whether preoperative radiotherapy can improve these surgical figures does not seem to have been definitely answered, although reviews have been made by Quan, Deddish and Stearns and a series is now being studied at St. Mark's Hospital in conjunction with the Radiotherapy Department of St. Bartholomew's Hospital. If no treatment of any kind is undertaken, the survival time is of the order of 27 months, while if colostomy is necessary for obstruction the average survival time from operation is only 17 months.

The size of the problem may be indicated by the fact that some 10 per cent of all cases are inoperable from general or local causes, while of those having a radical excision intended to be curative, 10 per cent developed pelvic recurrences and of those intended to be palliative 25 per cent developed pelvic recurrences. Thus, between 20 and 25 per cent of all patients with carcinoma of the rectum are likely to be candidates for radiotherapy and may be ex-

<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

pected to be referred for treatment in the presence of symptoms. In fact, the number referred is very much less, but if it is possible to show that these patients can be given substantial help there is no doubt that many more will be referred in the future.

Ralston Paterson's rather cynical conclusion is that the only cases of carcinoma of the rectum which do well with radiotherapy are either unproved histologically, or else are so small that they would probably have responded to almost any method of treatment, while even so the complications of intensive treatment are formidable. Many radiotherapists have been inspired to look for methods which will improve radiation response without undue disability to the patient and it is for this reason that a good many investigations have been made into the possibilities of combining various forms of medical treatment with radiotherapy.

It is not necessary to go into details of the wide variety of agents which have been administered over the years, but, since the introduction of 5 fluorouracil in 1957, it was soon found that this agent appeared to offer a number of advantages over its predecessors in the treatment of carcinoma of the lower alimentary tract, especially in carcinoma of the rectum, as it showed some degree of selective absorption in the intestinal mucosa and also appeared to be effective in adenocarcinoma as a tumor type. A number of cases has been treated with 5 FU alone with very encouraging results, but as practically all of them were very advanced, it is rather difficult to quote figures of any statistical value. Workers simply reported that most cases showed subjective improvement, many showed objective improvement and a few were unchanged, while the complications from intensive treatment were rather formidable, consisting of leukopenia, diarrhea, stomatitis and nausea. Its action as an antimetabolite, interfering with the synthesis of thymine from uracil and so retarding the formation of nucleic acids, is not so radiomimetic as the alkylating agents formerly used, so it seemed reasonable to use it in association with radiotherapy in the expectation that the two agents together would have an increased effect on the tumor.

The side effects of 5 FU were felt to be a great disadvantage in palliative treatment until it was found that toxicity could be greatly diminished by reducing the rate of injection. If the daily dose is given over 2 hours, diluted in 200 cc. of fluid, the side effects are practically as low as they would be with continuous infusion over the 24 hours. This causes considerably less discomfort to the patient, and also provides an interval in the day during which radiotherapy can be given.

The generally accepted safe dose of 5 FU is 15 mg./kg. body weight with a maximum of 1,000 mg. given daily for 5 days, followed by half this dose on alternate days for not more than 6 further doses, provided toxic signs do not supervene. It is usually considered inadvisable to give this dosage when there has been recent major surgery or wide pelvis irradiation or if the general condition of the patient is poor. In this present series, although most of the patients exhibited one or more of the classic signs of toxicity, in only 1 case did death appear to result directly from the treatment.

#### SCHEDULE OF TREATMENT

All patients were admitted to the hospital for treatment, but most of them were able to return home immediately afterwards.

After treatment, patients were examined at joint consultation clinics held with referring surgeons and the assessment of the results obtained is therefore a joint one. The injections were given during the mornings so that the patients were free for radiotherapy during the afternoons, except on Saturdays and Sundays, and a full blood cell count was carried out twice weekly during treatment.

Cobalt 60 treatment was given through a single posterior field in most cases, with field sizes varying from 8×12 to 10×15 cm.

and a tumor dose of 200 r per day was normally given for 3 weeks, totalling 3,000 r. No attempt was made to give really high doses of radiotherapy and it would seem unlikely that any marked beneficial effects would have followed the small tumor dose given without the supportive chemotherapy.

The total tumor dose of 3,000 r was not specially chosen in the first place, but the practice in this department is to aim for a tumor dose of 1,000 r per week and as the course of chemotherapy takes 3 weeks, cobalt 60 treatment was also given over this time in the first few cases. The results of these were so encouraging that there seemed little point in changing it, although from time to time higher tumor doses were given without any material improvement in the response. A similar scheme of treatment

is reported by Foye et al., giving smaller doses of both 5 FU and cobalt 60 teletherapy over a 2 week period, and Hodnett has reviewed 27 reports of this combination of treatment in a variety of tumors. Patients were given a low residue diet and were routinely prescribed anti-emetics and vitamins.

The cases here reported total 37, of whom 9 were female and 28 male, their ages varying between 40 and 84 years with an average of 64 (Table I). In 29 cases the rectum had been removed, and of the remaining 8 patients, 2 had been subjected to colostomy for obstruction and 6 had received no surgery but had been biopsied (Table II). Twenty of the operative procedures had been regarded at the time as radical while the other 9 were known to be only palliative as extension was already present at the

TABLE I
SUMMARY OF CASES

				Cobalt 60	5 FU		Complic	ations			Re	sults	
Case	Age and Sex	Surgery	Recurrence	Therapy (r)	Therapy (gm.)	Leuko- penia	Diar- rhea	Sto- matitis	Nau- sea	Relief	Objec- tive	Degree of Re- sponse	Survival Time
	54 M	Radical 1957	Bladder 1959	3,000	7	x	_	x	x	×	x	3	14 mo.
2	52 M.	Radical 1959	Perineum 1959	3,000	7	x	-	x	-	I	I	3	27 mo.
3	őr F	Palliative 1959	Pelvis 1959	3,500	7.5	x		x	x	x	-	2	8 mo.
4	62 M	~	Pelvis 1959	3,500	8	x	x	X	x	X		3	22 mo. 10 mo.
<b>5</b>	47 M	Radical 1958	Pelvis 1959 Pelvis 1960	3,500	7	x	_	x	x	1 🐧	_	2 0	3 mo.
	59 M 65 F	Palliative 1959 Radical 1957	Perincum 1060	3,000	7.5	Î	_	ÎÎ	Î	r	x	3	18 mo.
7	72 M	Radical 1957	Pelvis 1060	3,500	7'3	Ī	-	-	Ŷ	1 2	2	0	6 mo.
9	66 F	Radical 1959	Pelvis 1060	3,500	1 7	_	_	x	Ī	1	_	ī	II mo.
10	70 M		Pelvis 1060	3,500	6.5	r	x	I	-	x	x	3	16 mo.
11	42 M	Palliative 1060	Pelvis 1960	3,000	8	x	-		I	x	-	2	10 mo.
12	81 M	Palliative 1960	Pelvis 1960	4,000	7.5	-	-	x	-	x	-	2	13 mo.
13	57 M	Radical 1958	Perineum 1960	4,000	7	-		-	-	I	x	3	alive and well
14	51 M	Radical 1960	Pelvis 1961	4,500	8	I	-	x	X	x	-	2	22 mo.
15	67 F	Palliative 1961	Rectum 1961	4,000	7	x	-	X	I	-	1 -	0	3 mo.
16	64 M	Radical 1958	Pelvis 1961	3,700	7.5	-	-	-	x	x	-	2	18 mo.
17	69 F	Radical 1960	Spine 1961	3,000	6.5	-	-	-	x	I	×	3	alive and well
18	73 M	Radical 1957	Pelvis 1961	3,500	7.5	r	-	I	x	-	-	0	8 mo.
19	140 M	-	Pelvis 1061	3,000	8	x	×	1 =	I	x	X -	2	10 mo.
20	47 M	Palliative 1960	Pelvis 1062 Bladder 1062	3,500		X		X	x	X	1	2	15 mo. 21 mo.
21	6i M	Radical 1959 Colostomy 1962	Bladder 1962 Rectum (1962	4,500 3,500	7 7.5	x	x	Ŷ	Î	1	ı x	3 3	falive
22	58 F	Community 1902	1063	2,500		Î	î	Ŷ	x x	î x	1 -	2	{ <b>****</b> ****
23	74 M	Radical 1060	Perineum 1062	3,000	7	<del>-</del>		Ī	Ī	x	1 x	3	`12 mo.
24	63 M	Palliative 1062	Pelvis 1062	3,000		x		x	x	-	-	0	7 mo.
25	84 M		Rectum 1963	3,000	7 6	x	x	x	x	x	x	3	15 mo.
26	57 M	Radical 1958	Pelvis 11963	3,500	5	x	-	x	-	x	-	2	alive
			11964	2,500	6	x		x	x	-	-		_
27 28	64 M	Radical 1961	Perincum 1963	3,000	8		-	X	x	x	X	2	18 mo.
<b>2</b> 8	63 F	Palliative 1963	Pelvis 1963	3,200		x		ı x	×	I	-	3	alive and
29	51 M	Radical 1961	Spine 1963	2,500	8	-	-		-	x	x	2	12 mo.
30	59 M	Radical 1963	Pelvis 1963	3,000	8	x	-	×	<u>.</u>	-	-	0	3 mo.
31	76 M	Radical 1962	Pelvis 1963	3,400		x	- x	x	X	- x		0	died alive and
32	64 F		Rectum 1963	3,500	7.5			-			_	2	well
33	62 M	Colostomy 1963	Rectum 1964	3,000	8	x	×	x	×	x	I	2	alive and well
34	60 M	Radical 1960	Pelvis 1964	3,200	7	x	-	-	-	x	-	2	alive
35	53 M	Palliative 1964	Pelvis 1964	3,000	8	x	-	x	I	X.	-	2	alive
35 36	66 F		Rectum 1964	3,000	7	x	×	-	-	x	I	2	alive and well
37	78 M	Radical 1964	Pelvis 1964	3,000	8	-	-	-	-	x	-	2	3 mo.

Table II

PRIMARY SURGERY IN 37 CASES
(28 MALES, 9 FEMALES)

	1
Radical removal of rectum	20
Palliative removal	9
Colostomy	2
Biopsy only	6
	ı

time of operation; 7 of these latter cases were referred for immediate radiotherapy and chemotherapy. Complications due to the chemotherapy were observed in most of the cases, 29 having leukopenia below a 3,000 white blood cell count during the second or third week of treatment, 8 had diarrhea, 26 had stomatitis and 26 had nausea, but in no case was it necessary to interrupt treatment because of these complications, although their high incidence does, however, support the wisdom of treating these patients in a hospital (Table III). The single fatal case collapsed with pancytopenia and died 3 days after treatment, autopsy showing gross marrow aplasia.

### RESULTS OF TREATMENT

No attempt was made to regard treatment as curative, and, as many of the cases had lesions which were inaccessible to direct examination, it was necessary to rely largely on subjective reports of the patients' symptoms. Twenty-nine of the 37 cases experienced relief of symptoms of which pain was predominant, and in 17 of these it was possible to estimate objective improvement, either in the size of tumor or in diminution in the amount of bleeding or discharge (Table IV). The actual survival times are probably not significant in such a series when the object was alleviation of

Table III

COMPLICATIONS OF TREATMENT

Leukopenia (below 3,0∞)	29
Nausea and vomiting	26
Diarrhea	9
Stomatitis	26
Death	I

distress rather than eradication of disease, but it is noted that 10 patients are still alive and 6 of them have remained well to date; 2 after 4 years.

To summarize, good response was obtained in 12 cases, fair in 17, some response in 1, and 7 showed no response; I of these died immediately after treatment. Two cases might perhaps be mentioned in a little more detail, especially the first case treated, as the success in this case was directly responsible for continuing with the combined treatment. This patient was a man, aged 54 years, who had been subjected to a radical removal of the rectum in 1957 but who developed a recurrence in the base of the bladder and perineum in 1959, with severe pain and discharge, and marked dysuria.

After the course of combined treatment, his bladder symptoms cleared, with shrinkage of the area of invasion on cystoscopic examination. The perineal sinus completely healed, allowing him to spend over a year in comfort before he died of liver metastases. He was able to continue his business activities during the whole of this time, including his stay in the hospital. The second case of interest was a woman of 58 years who had a colostomy for subacute obstruction in 1962 and was referred for treatment as her general condition was too poor to permit excision of the growth. The first course was most successful, but symptoms recurred after 9 months and a further course was given. Since then the patient has remained alive and well for the last 2 years with some occasional bouts of bleeding and tenesmus but no further spread.

The cases treated have been analyzed

TABLE IV
RESULTS OF TREATMENT

Relief o		toms	29
Objectiv		ovement	17
	DEGRE	E OF RESPONSE	
(3) Good	12	(1) Fair	17
(2) Poor	1	(0) None	7 (1 death)

TABLE V
RESULTS BY SITES

	Good	Fair	Poor	None
Pelvis (2		12	I	5 (I death)
	6) 2 5) 4	3	_	
:	2) 2 2) I	-		—

according to the site of recurrence or residual disease (Table v). Twenty-two cases had a large part of the pelvis irradiated for unspecified spread with good response in 4 cases and fair response in 12 cases. Two cases with bladder deposits showed good response and in 6 cases the rectum itself was treated, with good regression in 2 cases, fair in 3, and none in 1 case. Of the 2 cases with spinal secondary lesions, 1 showed good response and 1 showed only fair response.

Deposits in the perineum were not normally treated with this combined technique as they usually respond well to direct irradiation, but of 6 so treated 4 showed good response and 1 fair response. This high rate of response when dealing with localized areas of recurrence is, of course, to be expected, but the good response of lesions in the rectum and bladder is encouraging and suggests that more might be done by giving repeated courses of treatment which, although possible technically, was only done twice in the present series.

### SUMMARY AND CONCLUSIONS

After a brief review of the present expectations from orthodox surgical and radiotherapeutic treatment in carcinoma of the rectum, a series of 37 cases is described in which treatment was given by a 3 week combined course of cobalt 60 radiation and systemic 5 FU with palliative results of an encouraging order. Treatment is being continued along similar lines with new cases

but investigations are also being made into the possibility of improving response with repeated courses of treatment similar to the split dose techniques described by Sambrook,<sup>7</sup> and with multiple courses as symptoms demand.

A few advanced cases have also been treated with intra-arterial 5 FU during an interval of irradiation, without any striking improvement as yet in response. The main conclusion to be drawn from this report is that there is strong evidence of synergism between radiotherapy and 5 FU and similar combined methods seem well worth investigating in the treatment of resistant tumors.

The Royal Sussex County Hospital Brighton, 7 Sussex, England

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### APPARENT BONE AGE IN CANCER

By JOSEPH STEIN, M.D.,\* and JOHN L. SMITH, M.D.,† LONG BEACH, CALIFORNIA

HE determination of bone age in children is a well established roentgenologic procedure. The estimation of adult bone age is a less exact evaluation; however, numerous attempts have been made to establish criteria for normal bone aging. Apparent bone density, degree of osteophytosis, alignment of vertebral bodies, etc., have all been used to estimate bone age. During the process of evaluating bone aging in the adult male veteran population, we have been impressed by the large number of patients with neoplastic disease who presented an apparent bone age considerably younger than their chronologic age. It is the purpose of this paper to review our experience with the apparent young bone age of patients with malignant neoplastic disease.

The judging of adult bone age is not a new concept. In the past, many observations have been made concluding that the aging skeleton develops hypertrophic and atrophic changes consistent with a given age.

Bohatirchuk¹ discussed the roentgenographic changes in the aging vertebrae, emphasizing two signs of bone atrophy, namely, the generalized decrease of roentgen-ray absorption and the morphologic changes of atrophy. Bohatirchuk¹ thought that the rough estimate of the radiologist's eye was the best method to rate the general decrease in roentgen-ray absorption. Different ages will produce different degrees of bone atrophy and as the vertebral body ages, there is thinning of the cortex, prominent trabecular pattern and more contrast between the cortex and the spongiosa.

Bohatirchuk also used osteophytosis as a guide in evaluating the aging vertebral

column, there being evidence of hypertrophic changes in the vertebral bodies in 60 to 80 per cent of the population. Under the age of 60 years, hypertrophic lipping was mostly symmetric, while in advanced ages the lipping became asymmetric.

Nathan<sup>8</sup> reviewed osteophyte formation according to age, race and sex. He studied 400 skeletons and classified the degree of osteophytosis according to severity and location. He found that by the age of 20 years, a large proportion of the vertebral bodies already had anterior osteophyte formation. By the early forties, 100 per cent of the skeletons had anterior osteophyte formation. The degree of severity of osteophyte formation varied with the age. At 50 years all skeletons evidenced moderate osteophyte formation, and by the age of 80 there was a severe degree of osteophyte formation.

Meema<sup>6</sup> evaluated a large number of patients and demonstrated a gradual thinning of the cortex with age in both sexes. There was a positive correlation between the degree of cortical bone atrophy and osteoporosis of the spine. Senile osteoporosis was a normal manifestation of normal aging and the most important single factor was the decrease in the gonadal function with aging.

Bone appearance alters with age and the greater the age the greater will be the bone change. We found that the most reliable criteria for bone age estimation were (1) the degree of bone atrophy as evidenced by osteoporosis or decreased bone density, and (2) the degree of bone hypertrophy or osteophytosis. After the age of 40 the first definitive roentgen signs of bone aging began to appear. In older patients the degree

<sup>\*</sup> Chief, Diagnostic Section, Radiology Service, Long Beach VA Hospital; Associate Clinical Professor (Radiology), California College of Medicine.

<sup>†</sup> Assistant Chief, Radiology Service, Long Beach VA Hospital; Assistant Clinical Professor (Radiology), California College of Medicine.

of atrophy and osteophytosis appeared to parallel the chronologic age. As we gained experience, we became more accurate in correlating the bone age with the stated age of the patient. However, occasionally the bone age estimates were remarkably lower than the stated age of the patient (Fig. 1 through 3). In an effort to discover why the age discrepancy was present, we investigated the "young bone age" patients and discovered that a considerable percentage of these patients carried a diagnosis of cancer.

#### FINDINGS

Two hundred male veteran patients were selected at random and roentgenograms were taken of the lumbar area in anteroposterior and lateral projections. The only requirement that was made in selection was that the patients had no history of back pain.

Of the initial survey (200 patients), 33 patients were found to have unusually young bones by roentgenograms when compared to their chronologic age. Of these 'young bone" patients 14 or 42 per cent were subsequently found to have cancer of a major organ. Skin cancer was not included in this group. One hundred and sixty-seven cases were judged to have normal or physiologic bone age. The normal bone age group contained 16 cancer patients or 9.6 per cent. In other words, the "young bone age" group proved to have an incidence of cancer 4 times the normal bone age group. These results are shown in Tables 1 and 11.\* The difference between

TABLE I

	Young Bones	Normally Aged Bones	Totals	
Cancer No Cancer	14 (42%) 19 (58%)	16 (9.6%) 151 (90.4%)	30 170	
Totals	33	167	200	

TABLE II

	Young Bones	Normally Aged Bones	Totals	
Cancer No Cancer	12 (44%) 15 (56%)	15 (26%) 42 (74%)	27 57	
Totals	27	57	84	

9.6 per cent and 42 per cent in Table 1 was tested for significance using the t-Test and found to be significant at the .or level; that is, the chances are 99 to 1 against this being simply a chance difference. However, these two data had 2 weaknesses. In the first place, the age difference between "young bone" patients and normally aged bone patients was 13 years (average ages 67.8 vs. 55.1), suggesting that the greater incidence of cancer in "young bone" patients occurred simply because they were chronologically older. In the second place, this sample contained outpatients for whom the diagnostic work-up was not as complete as for inpatients. Consequently, all outpatients and all patients under 50 years of age were eliminated from the study.

This reduced the sample to a total of 84 patients as shown in Table II. It is noted that the average of "young bone" patients was 68 and that of patients with normally aged bones was 66. This difference is statistically insignificant. The difference between the incidence of cancer among young bone patients (12/27 = 44 per cent)and old bone patients (15/57 = 26 per cent) was tested statistically using the t-Test. It was found that this difference was significant at the 10 per cent level. While this is below the usually accepted 5 per cent or I per cent level of confidence, it is at least suggestive of a relationship between bone age and the incidence of cancer.

### DISCUSSION

The high incidence of carcinoma in patients with "young bone age" appears at first to be a paradox. Carcinoma is asso-

<sup>\*</sup> Statistical analysis by George F. Seacat, Ph.D., Chief, Psychology Service, Long Beach VA Hospital.

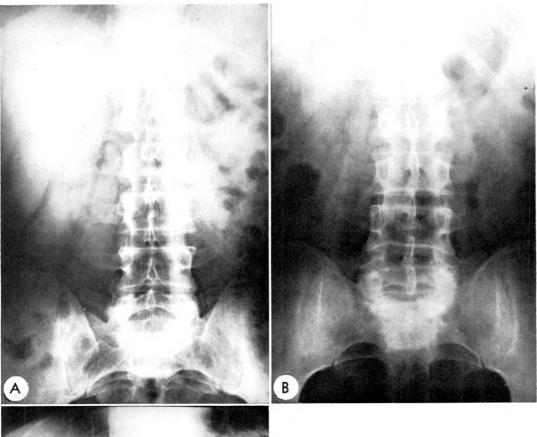
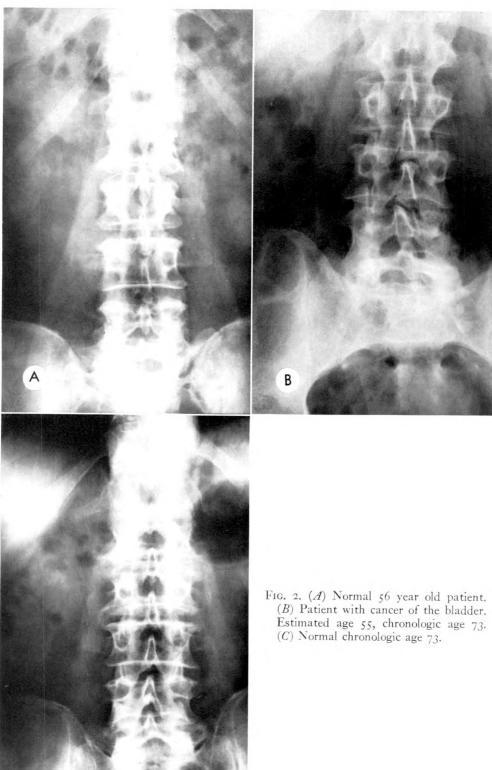




Fig. 1. (A) Normal 49 year old patient. (B)
Patient with cancer of the rectum. Estimated age 50 years, chronologic age 69.
(C) Normal chronologic age 69.



ciated with the aged, and the presence of "young bones" would tend to indicate lack of aging and, therefore, less likelihood of cancer. However, during the past decade the oncologists and endocrinologists have become aware of the occurrence of several endocrine syndromes in association with neoplasia. There is evidence that some neoplasms produce hormones (or hormone-like material). Ordinarily, these hormones are those produced in organs other than the site of origin of the neoplasm.

Each normal cell of the body is endowed with DNA; however, there are specific controls that prevent a cell from utilizing all of the information coded on its complement of DNA. Neoplastic transformation of a cell may permit synthesis of proteins and peptides that are ordinarily repressed. The production of highly complex molecules by a neoplastic cell may represent loss of control mechanisms that are normally present.

Para-endocrine syndromes with neoplastic disease are surprisingly common. Lipsett *et al.*<sup>4</sup> reported a large number of cases of carcinoma with varying types of hormone production.

There are many reports in the literature showing hypercalcemia in neoplasia.<sup>5,9</sup> Many of these cases returned to normal calcium levels following removal of the cancer.<sup>2,4,7</sup>

Greenberg et al.<sup>8</sup> reviewed the literature, stressing unusual systemic manifestations associated with carcinoma. They thought that there was support for the concept that some primary tumors secreted a parathyroid-like substance, creating hypercalcemia without apparent bone metastasis.

Thus, there is increasing evidence that neoplastic cells are capable of producing hormone-like substances. Many of these substances appear to resemble gonadal hormones in their action. High doses of gonadal hormone produce hypercalcemia. Senile osteoporosis is primarily a manifestation of normal aging, and as gonadal function decreases there appears to be a related increase in the degree of aging. However,

in the event neoplastic disease intervenes and produces hormone-like substances (gonadal?), there appears to be cessation of the normal bone aging and many of the cancer patients present the "young bone" picture. This may indicate that a longstanding hormonal environment was present, possibly because of an occult neoplasm which caused cessation of bone aging even before the neoplasm itself became clinically manifest. There is also the possibility that an unusual hormonal environment preceded the neoplasm and was contributable or responsible for development of cancer. These possibilities may warrant investigation.

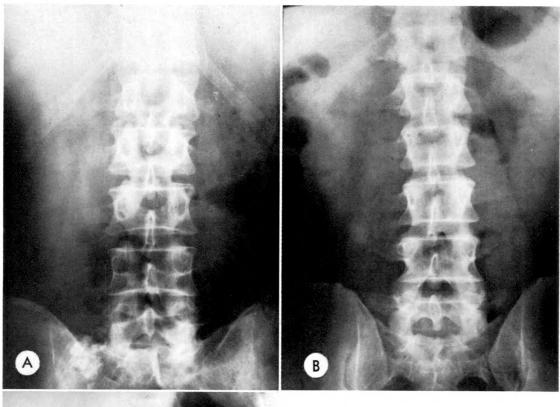
If any serious clinical application of our findings is to be made, more work is needed on a standard method of estimating adult bone age. At the very least, rough guide lines should be set forth to categorize the normal age groups according to the bone appearance.

### SUMMARY

A survey of the bone age of 200 patients is presented. The bone age was grossly underestimated in 33 patients. Of these patients with "young bones," 42 per cent had cancer, while in the so-called normal bone age group only 9.6 per cent had cancer. The incidence of cancer in the "young bone" group is 4 times as great as in the normal bone age group. The finding of "young bones" in older patients warrants further investigation to exclude unsuspected cancer. Speculation is made as to whether the "young bone" patients represented the result of a hormone secreting cancer or whether this group represented an unusual hormonal situation particularly prone to develop cancer.

Joseph Stein, M.D. Radiology Service Veterans Administration Hospital 5901 E. Seventh Street Long Beach 4, California

We wish to express our appreciation to Bernard H. Feder, M.D., Chief, Radiology Service, Long Beach VA Hospital and



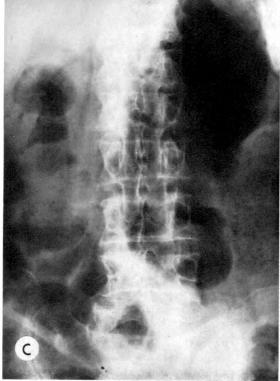


Fig. 3. (A) Normal 40 year old patient. (B)
Patient with Hodgkin's disease. Estimated age 40, chronologic age 69. (C)
Normal 69 year old patient.

Associate Clinical Professor (Radiology), U.C.L.A. Medical School, and to Bernard J. O'Loughlin, M.D., Professor and Chairman of the Radiology Department, California College of Medicine, for their assistance in reviewing and editing this manuscript.

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## A CRITICAL ANALYSIS OF STRONTIUM BONE SCANNING FOR DETECTION OF METASTATIC CANCER\*

By N. DAVID CHARKES, M.D., DAVID M. SKLAROFF, M.D., and IRVING YOUNG, M.D. PHILADELPHIA, PENNSYLVANIA

ETASTASIS to bone in patients dying of cancer ranks second only to metastasis to lymph nodes, lung and liver in frequency of occurrence as noted at postmortem examination. In patients with tumors which commonly metastasize to bone (prostate, breast, lung), osseous involvement occurs in perhaps 85 per cent of cases seen at autopsy.9 Nevertheless, the roentgenographic diagnosis of metastatic cancer in trabecular bone is often unsatisfactory because calcium content must be decreased by about 30 to 50 per cent before observable roentgenographic changes occur. Lesions must be approximately I to 1.5 cm. in diameter in vertebrae before they can be appreciated on a roentgenogram.8

When radioisotopes became available for diagnostic use in humans, considerable attention was focused upon the problem of metastatic cancer in bone. Strontium 89 was found to be deposited in and around osteogenic sarcomas,20 and later radiogallium 72 and radiophosphorus 32 were used. Calcium 47 has also been employed by some groups. In the doses used, none of these radionuclides has physical characteristics suitable for photoscanning. Strontium, because of its similarity to calcium in bone metabolism, has been extensively studied through one of its radioisotopes, 64 day Sr85, the 513 kev. photon of which is readily collimated by commercial detectors. Since there are no other radiations in the decay process, Sr85 is well suited for photoscanning.4,6,8,14,16,17,18

Strontium 87m (388 kev. 2.8 hour half-life) has also been investigated and found

to be acceptable for diagnostic clinical scanning studies.<sup>5,11</sup> We have recently reviewed the subject of strontium bone scanning in some detail.<sup>6</sup>

To date, we have made more than 350 strontium 85 scans in patients with malignant disease with proven or suspected bone metastases. Twenty-six of these patients have undergone diagnostic bone biopsy in scanned areas, and tumor cells were identified in 21. Eleven of these biopsy specimens were counted in the well-scintillation counter and the Sr85 concentration was determined as the per cent of the administered dose per gram of bone. In 3 cases, multiple sections were made through a bone, and the histopathologic changes were correlated with the concentration of Sr85 as determined by scanning and by well-scintillation counting.19

The biopsy findings revealed a marked similarity, in regard to the site of radiostrontium deposition, between newly formed bone produced in reaction to tumor invasion and the growth zones of normal bone. In young animals, radioactive strontium is normally taken up by immature, poorly mineralized osteoid in the areas of growth. As calcification proceeds, the rate of radiostrontium deposition decreases, and older, highly calcified bone shows no radiostrontium uptake. 10

Bone often reacts to the presence of tumor by proliferation (reactive bone formation)<sup>13,15</sup> and the histologic picture then is usually one of mixed destructive and reparative processes. The biopsy specimens showed a high degree of correlation be-

<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8–10, 1965. Part of the symposium, "Critical Analysis of Some Diagnostic Tests Using Radioactive Isotopes," Chairman: Dr. Edith H. Quimby.

From the Departments of Radiology (Nuclear Medicine & Radiation Therapy) and Pathology, Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania.

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Table I

CORRELATION OF STRONTIUM SCAN, ROENTGENOGRAM AND HISTOPATHOLOGY

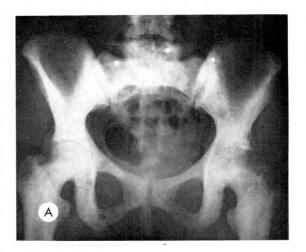
Phase Histopathology		Strontium Uptake	Roentgenogram		
Ι	Bone destruction and immature reactive bone (young osteoid)	Marked	Bone destruction (radiolucencies); bone formation may be invisible at this stage		
II	More mature reactive bone (partially mineralized)	Considerable	Mixed destruction and formation (radiodensities)		
III	Old, highly calcified reactive bone	Minimal	Radiodense		

tween strontium deposition and the presence of immature reactive bone formed in areas of tumor invasion (Table 1).<sup>19</sup> At this stage roentgenographic changes are minimal but the scan is "hot." As bone matures and the osteoid seams mineralize, radiodensities appear on the roentgenogram and the scan remains positive (Fig. 1). However, fully mineralized reactive bone takes up little additional radiostrontium despite its great density on the roentgenogram (Fig. 2, A and B), which

Fig. 1. This 71 year old female underwent radical mastectomy 9 years previously for cancer and recently complained of low back pain. Roentgenograms revealed radiodensities in lower dorsal vertebrae. Increased strontium uptake is seen in these vertebrae on the bone scan, with extension into the heads of the 7th, 8th and 9th ribs on the right.

may give rise to a "false-negative" scan reading.

Thus, the strontium bone scan correlates well with the histologic activity of the bone



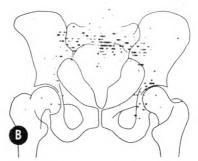


Fig. 2. Breast cancer patient 7 years post mastectomy, asymptomatic and on no therapy. (A and B) Extensive bone involvement on roentgenogram contrasts with minimal activity on scan (in sacrum, sacroiliac joints, and left ischium). Scan reflects clinical and histologic activity of process. (Reprinted with permission from Progress in Clinical Cancer, Grune and Stratton, Inc., 1965.)

lesion: areas of tumor growth may give rise to pain and "hot" Sr<sup>86</sup> scans despite minimal roentgen changes, whereas older, quiescent lesions may appear normal on scan but are radiodense.

In a small number of patients (about 2 per cent of our series), we obtained negative strontium scans in areas of known bone metastasis, almost always presenting as radiolucencies on roentgenogram. These patients had anaplastic malignancies (reticulum cell sarcoma-3, carcinoma of lung-1) or breast cancer (stable-1, progressive-1). Anaplastic tumors may incite little or no new bone formation despite widespread destruction. Biopsies in these 6 cases failed to reveal any reactive bone.

Strontium bone scanning is of proven clinical value in the cancer patient under these circumstances:

- 1. With bone pain, usually in the back, when roentgenograms are normal or show minimal or equivocal changes (Fig. 3). Often the roentgenologist can more accurately interpret borderline findings after having seen the scan.
- 2. In determination of the extent of bone disease when a minimal lesion is identified on the roentgenogram (Fig. 4, A-D), particularly in the asymptomatic patient.
- 3. In evaluation of areas difficult to study accurately by roentgenogram, such as the sternum.
- 4. For finding a site suitable for diagnostic bone biopsy in the cancer suspect (Fig. 5, A and B).
- 5. In differentiating traumatic from pathologic fracture by demonstrating multiple sites of bone involvement not visible on roentgenogram.
- 6. In evaluating the degree of bone involvement by meningiomas.<sup>4</sup>
- 7. In planning treatment portals (Fig. 6, A, B and C).

In addition to these proven uses, we are currently investigating other possible uses for strontium bone scans:

9. Measurement of the response to radiation therapy or hormonal and/or

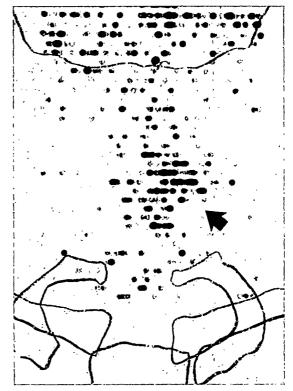


Fig. 3. R.S., 30 months post mastectomy for cancer, developed peripheral neuropathy of left arm. Roentgenograms revealed only degenerative changes, but scan showed "hot spots" in cervical spine to the left of the midline (arrow). Radiation therapy to scan lesion completely relieved the neuropathy. Generalized bone metastases later developed.

chemotherapy prior to roentgenographic changes.

- 10. Evaluation of the bone response in multiple myeloma. Positive bone scans in this disease<sup>6</sup> indicate that reactive bone formation may be more common than is usually thought.
- 11. Determination of the presence of metastatic bone disease in breast cancer patients, as a criterion of inoperability. External counting has been successful in this regard.<sup>11</sup>

Strontium bone scanning is performed with a conventional, unmodified commercial scanner. The resolution of the method is quite satisfactory for clinical purposes. We inject 100  $\mu$ c of Sr<sup>85</sup> (Strotope, E. R. Squibb & Sons) intravenously and wait

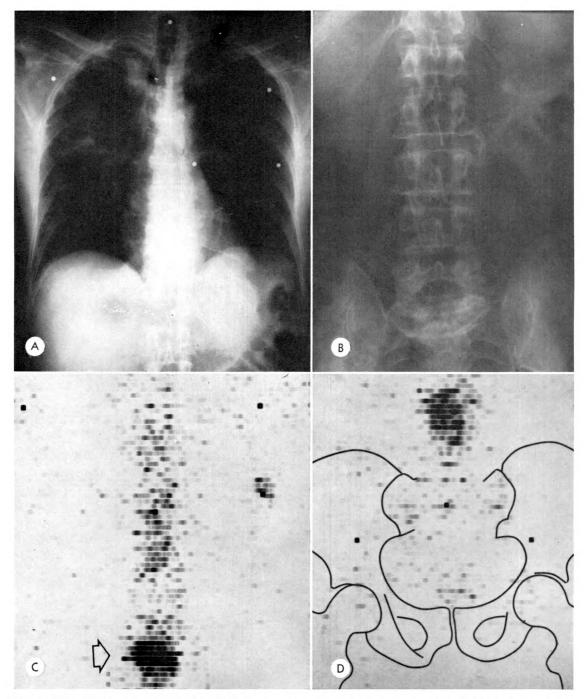


Fig. 4. This elderly male developed multiple bone metastases to the dorsal spine and ribs from an anaplastic carcinoma of the lung (A). His chief complaint was low back pain. (B) Roentgenogram of lumbar spine shows osteoarthritic changes and compression of L-I. (C and D) The strontium scans, in addition to showing numerous areas of abnormal uptake in the dorsal spine, rib, and in L-I (arrow in C) revealed activity in L-3 and -4 as well, despite negative roentgenographic findings in this area. Radiation therapy to the lumbar spine relieved the patient's pain. This case shows the value of the strontium bone scan in determining the extent of metastatic disease.

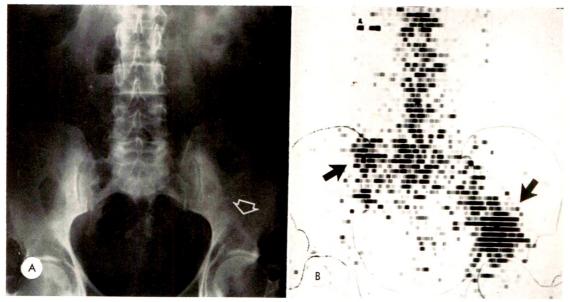


Fig. 5. This 55 year old male developed pneumonia and back pain due to collapse of D-5. Carcinoma was suspected but bronchial washings were negative for tumor. (A) Bone survey roentgenogram of pelvis was thought to be normal but (B) Sr<sup>85</sup> scan revealed "hot spots" in left ilium and right sacroiliac joint (arrows). Biopsy of left iliac lesion showed anaplastic carcinoma. In retrospect, the "washed-out" appearance above the left acetabulum (arrow) is a radiolucent metastasis.

48 hours to allow for excretion of sufficient undeposited radiostrontium<sup>2</sup> to permit satisfactory scanning. Most of the radiostrontium is deposited in bone within an hour after injection so that early scanning may be attempted in an emergency.<sup>5</sup> However, high blood background at this time makes it more difficult to evaluate some bone lesions and the later scanning time is preferable. The bowel must be thoroughly cleansed with laxatives and enemas prior to scanning since fecal Sr<sup>85</sup> overlying the

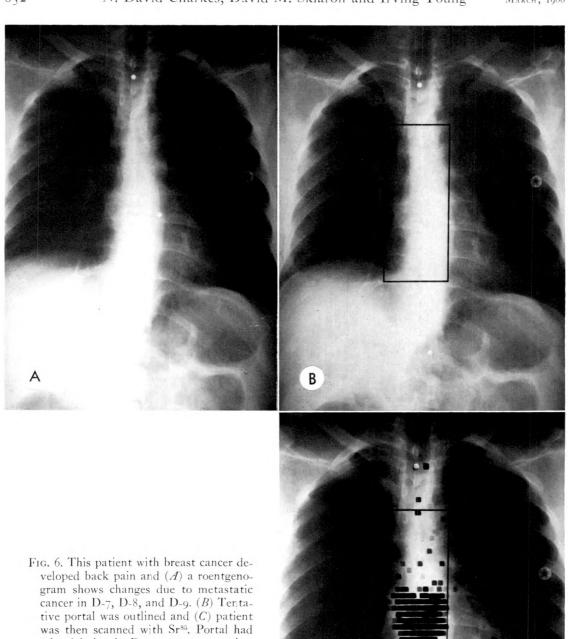
spine or pelvis may simulate a tumor metastasis (Table II). The scan is localized by means of a 6 foot recumbent roentgenogram.

It must be recalled that the deposition of strontium in bone is a nonspecific process, so that other diseases which produce reactive bone will also give a positive scan (Paget's disease, osteomyelitis, fracture, benign bone tumors, etc.).

"False-negative" scans, as mentioned, are rare (Table III). Certain slowly growing

Table II
"false-positive" strontium bone scans for tumor

Condition	Roentgenogram	Remarks		
A. Nonmalignant diseases (Paget's disease, osteomyelitis, benign tumors, fracture, etc.)	Characteristic for the disease			
B. Sr <sup>85</sup> in colon	Normal or barium-filled colon	Repeat scan after enemas and laxatives		
C. Joint looks "hot"	Normal	Normal strontium deposition		



missed lesion in D-12 seen on scan but not visible on roentgenogram; it was then reset to include this lesion.

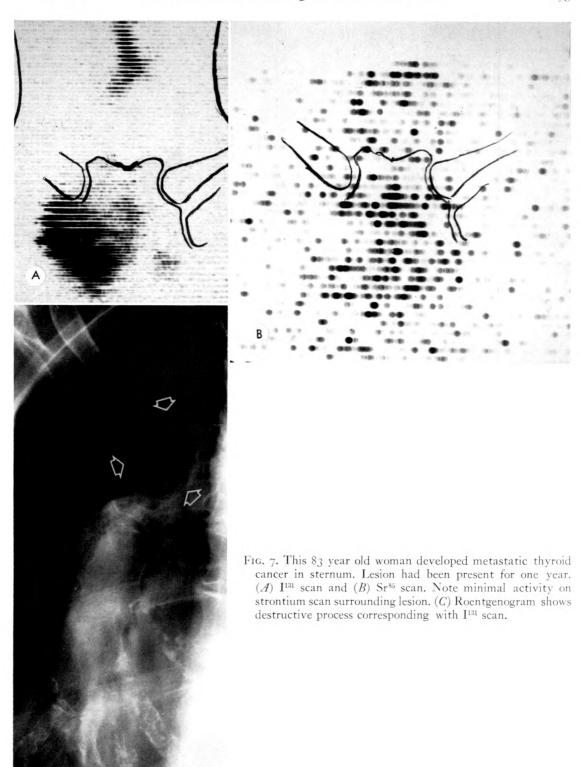


Table III
"false-negative" strontium bone scans for tumor

Disease	Disease Roentgenogram	
A. Highly anaplastic tumors (reticulum cell sarcoma, etc.)	Radiolucent	No reactive bone
B. Stabilized lesions (breast, thyroid, etc.)	Radiolucent or radiodense	See Table 1
C. Minimal tumor growth	Negative or equivocal	Rescan in several days to 1 week
D. Diffuse metastases to spine	Any	Get ratio of counts of mid-dorsal spine to tibia

metastases produce little bone reaction and the scan shows correspondingly minimal changes (Fig. 7, A, B and C). In other cases, a "false-negative" scan becomes positive if the patient is rescanned several days later so that nonosseous Sr<sup>25</sup> background is reduced via urinary and fecal excretion (Fig. 8, A, B and C).

Occasionally, patients with diffuse disease of the spine are scanned and the pattern cannot be differentiated from the normal since the over-all distribution of uptake is unchanged. It is advisable to take counts over the mid-dorsal spine and compare with counts over the tibia in such patients, the normal ratio having already been established. With metastasis to the spine, the ratio is elevated. <sup>21</sup>

Despite the disadvantages of Sr<sup>85</sup> (Table IV) which have prompted the investigation of Sr<sup>87m</sup> as an agent for bone scanning,<sup>5,11</sup> Sr<sup>85</sup> has proven to be an effective isotope for detection of occult bone metastases.

Table IV

DISADVANTAGES OF ST<sup>85</sup> FOR BONE SCANNING

1. Long physical half-life (64 days) and slow turnover rate in bone preclude repetitive studies

Radiation dose to bone (1.6-4.6 rads per 100 μc injected) limits dose to 100 μc, resulting in long scanning times and suboptimal resolution

3. Fecal excretion requires bowel cleansing

4. Forty-eight hour delay after injection is advisable

5. AEC approval for study of malignancy only

The merits and drawbacks of Sr<sup>87m</sup> have been discussed elsewhere.<sup>5</sup>

### SUMMARY

Evaluation of more than 350 bone scans in cancer patients with proven or suspected metastases has shown Sr<sup>85</sup> to be an effective agent for the detection of occult tumors. Biopsy studies in 26 patients indicate that radiostrontium deposits in the new bone formed in reaction to the presence of cancer. Specific uses of bone scans, pitfalls in interpretation, and disadvantages of Sr<sup>85</sup> are discussed.

N. David Charkes, M.D. Division of Radiology Albert Einstein Medical Center York and Tabor Roads -Philadelphia, Pennsylvania 19141

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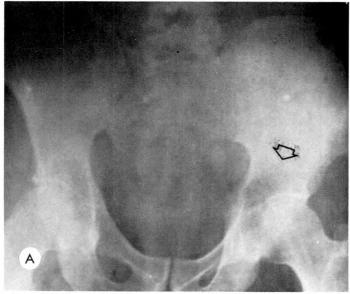
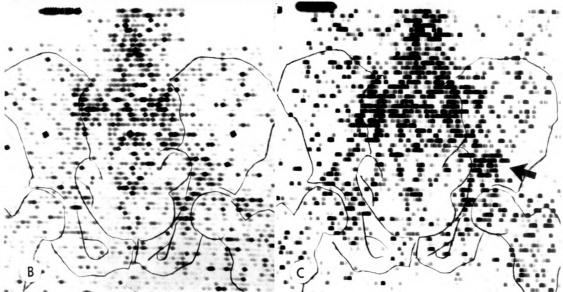


Fig. 8. (A) Metastatic melanosarcoma to ilium with equivocal roentgenographic changes (arrow). (B) Sr<sup>85</sup> scan 2 days post dose was read as probably positive, but "hot spot" is clearly seen in (C) scan repeated 7 days later (arrow).



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## A STUDY OF THE MORPHOLOGY OF THE NORMAL PANCREAS USING Se<sup>76</sup> METHIONINE PHOTOSCANNING\*

By E. RICHARD KING, M.D., ALTON SHARPE, M.D., WALTER GRUBB, M.D., JULIAN S. BROCK, M.D., and LEONARD GREENBERG, M.D.
RICHMOND, VIRGINIA

THERE are certain approaches in the attempt to visualize on paper, film, or tape, the size, position and morphology of organs and body systems. The technique discussed here involves outlining an organ, the pancreas, by detection of emissions from radionuclides located within the structure of this organ. The mode of placing or locating such radioactive nuclides or labeled compounds in different organs or systems can vary. We believe a brief discussion of basic techniques is applicable.

From a theoretic standpoint, organ visualization using radionuclides or compounds with radioactive labels involves either an active or passive placement of these materials within the structure to be studied.

### ACTIVE BIOLOGICAL LOCALIZATION

The term active localization implies a biological or metabolic deposition of the radioactive material in the organ or system to be studied. The most common of the elements needed in the formation and growth of the biological systems; namely oxygen, carbon, hydrogen, nitrogen and sulphur are not discussed since radionuclides of this group of elements do not have the physical characteristics insofar as radiation emissions and physical half life are concerned to make them applicable for studies involving external counting procedures.

Examples of active biological localizations are:

1. Using radioisotopes of an element that is actually incorporated into the structure of the organ to be studied, such as radio-

calcium which is a normal constituent of apatite crystals of new or replaced bone. Radioisotopes of strontium behave similarly to calcium although this element is not normally utilized in bone formation.

- 2. Another method of active biological localization is to substitute radionuclides for stable atoms needed in the synthesis of products of the various exocrine and endocrine glands. The most well-known example of this is the use of radioiodine in the diagnosis and treatment of thyroid disorders. The iodine, stable or radioactive, is biologically localized in the thyroid as it is needed for synthesis of the thyroid hormones.
- 3. Active biological localization can also be performed by the action of some systems in removing foreign and particulate materials from the circulating blood. The reticuloendothelial system which is located in such organs as the liver, spleen and bone marrow is an example. Thus colloidal Au<sup>198</sup> particulates are removed from the vascular stream by cells of this system in the liver, and if the liver is diseased, by the spleen and bone marrow reticuloendothelial system.
- 4. Certain organs produce biological cells and structures. The bone marrow is the site of development of the erythrocyte, the leukocyte and the platelet. Radioactive iron is removed from the blood and incorporated into the hemoglobin of the forming red blood cell. Also, certain organs act as a graveyard for biological structures. The normal spleen removes and breaks down old erythrocytes. Thus labeled red blood cells rendered prematurely fragile are removed

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Part of the symposium, "Critical Analysis of Some Diagnostic Tests Using Radioactive Isotopes." Chairman: Dr. Edith H. Quimby.

From the Department of Radiology, Medical College of Virginia, Richmond, Virginia.



Fig. 1. Pancreas scanning morphology. Impressions of the shape of the pancreas as determined by photoscanning with Se<sup>76</sup> methionine.

from the blood stream and their labels may be used to outline the site, shape and size of the spleen.

5. Other systems have a protective function such as the so-called "blood brain barrier." Here the function appears to prevent foreign materials from circulating through the brain. If the system is disrupted, either by trauma or by a space-occupying lesion, these foreign materials locate at the site of disruption. If these foreign elements or compounds are gamma emitting radionuclides, the site of localization may be easily detected by external radiation detecting instruments.

### PASSIVE BIOLOGICAL LOCALIZATION

The nonphysiological approaches to radioisotopic scanning are as follows:

- 1. The injection or instillation of a radioactive material directly into the organ or system to be studied. To date, this approach has usually been performed with stable radiopaque materials, such as in percutaneous cholangiography or splenoportography. Another example is the injection of a radioactive compound into the peritoneal cavity to outline its extent.
- 2. The injection of a radiopaque or radioactive material into the vascular supply of an organ or system, and thus trace its outline and position. Radioactive lymphangiography has been performed in this manner with colloidal Au<sup>198</sup> or with I<sup>131</sup> ethiodized oil.

3. One can also place the material, again it may be radiopaque or radioactive, into the lumen of the organ or structure through an orifice. Most common of this type of study are the barium enema examination, gastrointestinal series and retrograde pyelograms of diagnostic radiology.

### SELECTION OF A METHOD OF VISUALIZING THE PANCREAS

The pancreas presents special problems and has always been an enigma to physicians. This irregular, friable organ, quickly digested by its own enzymes at death, is almost impossible to study at autopsy. Its retroperitoneal position, hidden behind the huge parenchymatous liver with the food and feces filled stomach and intestine acting as a moving shield, makes it difficult to approach and almost impossible to see in its entirety by the surgeon. The internist is only becoming aware of its full importance and functions and lacks adequate tests for its normal physiology. The diagnostic radiologist approaches the study of this organ with frustration, for it is one organ he cannot visualize on a roentgenogram.

For these reasons great efforts have been made over the past years to produce the outline of this organ on roentgenograms. All attempts at passive localization have proved inadequate, although there are investigators who still feel that this approach has possibilities.

Since this organ is both an exocrine, as well as an endocrine gland, efforts to supply a radionuclide to the gland that would be incorporated by biosynthesis into one of its endocrine or exocrine products appear to offer the best hope of pancreatic visualization. Since insulin contains zinc, and Zn<sup>65</sup> has good physical characteristics as a biological tracer, several studies along this line have been reported, but as of this date, they do not appear to produce adequate results.<sup>8,5</sup>

It is well known that the pancreas very actively utilizes amino acid in its metabolism, especially for production of its exocrine enzymatic secretions. When Blau and

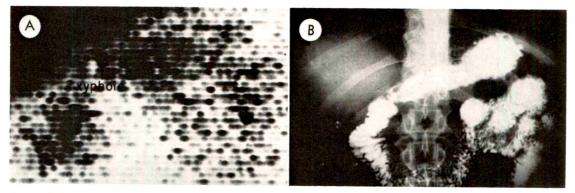


Fig. 2. (A) A scan of the pancreas using the technique as described in the text. Immediately following the scan an upper gastrointestinal series was performed and a spot roentgenogram (B) was made. If superimposed, the portion of the scan believed to represent the "head" of the pancreas fits well into the duodenal loop. The body and tail lie behind the greater curvature of the stomach and the loop of jejunum seen in B.

Bender<sup>1</sup> reported that they had produced a labeled precursor of the exocrine products, the pancreatic enzymes, that could be detected by external counting, the response was enthusiastic. These investigators by great ingenuity misled yeast into substituting selenium 75 for stable sulphur when the veast biosynthesized the amino-acid methionine. Thus Se<sup>75</sup> methionine was produced, a substance readily utilized by the pancreas in its synthesis of enzymes. Methionine does not occur in insulin or glycogen but is in high concentration in the exocrine enzymes of the pancreas. (It makes up 1.2 per cent of the chymotrypsinogen molecule.) It was hypothesized that the concentration of Se75 methionine in the pancreas would be sufficiently high to outline that organ by routine scanning procedures.

Efforts to obtain early localization of this amino acid in the pancreas with retention of the labeled enzymes until a scan could be made, however, proved disappointing. In addition, the overhanging liver localized and metabolized the Se<sup>75</sup> methionine. In their basic studies, Blau and Manske<sup>2</sup> showed that the activity per gram of this labeled amino acid was less in the liver and surrounding organs than in the pancreas. However, because of the liver size, the total percentage of the compound in the liver was much greater than that in the pancreas and this created an additional

problem in the delineation of the liver and pancreas on the scan.

Instrumentation seemed to furnish no great problem since a good selection of probe and crystal sizes and various types of collimators is available for scanning purposes; however, for optimal uptake a preparatory diet appeared necessary.

Blau and Bender<sup>1</sup> planned a diet by which the pancreas was stimulated to remove the labeled amino acid from the blood stream, synthesize the enzyme and hold the enzyme long enough so that the pancreas could be outlined on the scan. They originally used Vitrum (Sweden), a mixture of secretin, pancreatozymin and cholecystokinin. When secretin became unavailable for clinical use, other investigators developed different preparatory meals. Sodee7 used a high protein meal and later added glutamic acid hydrochloride. Rodriguez-Antúnez6 added morphine sulfate, parenterally, to constrict the sphincter of Oddi. Hutner,4 after trying various preparatory meals discarded them all, and performed his scans without preparation, and obtained satisfactory results.

During the past year, we have attempted to outline the size, position and shape of the normal pancreas. A few scans performed in 1962 using Blau and Bender's original preparatory diet with the substitution of whiskey for secretin revealed a great disparity in the shape of the pancreas.

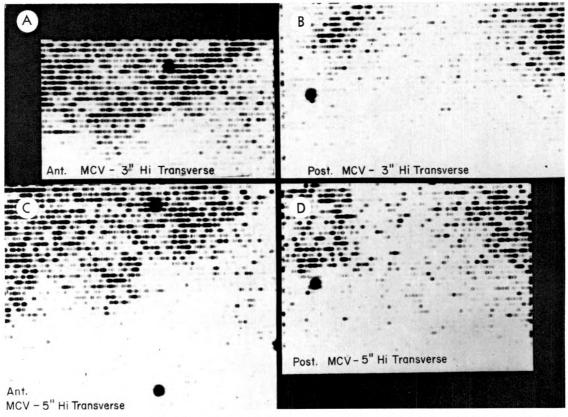


Fig. 3. (A-D) A comparison of supine (anterior) and prone (posterior) scans using the 3 inch (A and B) and 5 inch (C and D) crystal scanners with 3 inch focusing collimation. The technique described in the text was used. The large dot in the upper scans in A and C and the left-mid scans in B and D represents the xyphoid process. It can be noted that the supine (anterior) position produces the best result and that the 3 inch crystal scan is better than the 5 inch crystal scan. These scans were all performed in the same patient on the same day with repeated doses. This patient had a pancreas of the morphology we described as "high transverse."

### MATERIALS AND METHOD

A total of 33 adult normal patients had pancreas scans performed. The patients were males and nonpregnant females over the age of 21. Mostly, they were sanatorium patients who had no history suggestive of pancreatic dysfunction. There were no positive physical findings or laboratory data to indicate pancreatic disease.

Results obtained by using the 3 inch probe with the 3 inch broad focusing collimator and the 5 inch probe with the 3 inch broad focusing collimator were compared. Also simultaneous dot scans and photoscans were obtained, and studies with the patient prone were compared with studies in the supine position. In our hands, the

3 inch probe and 3 inch broad focusing collimator with the patient in the supine position produced the best results. Our best scans were made after the use of the Blau and Bender diet with oral whiskey substituted for intravenous secretin, and by starting the scanning procedure  $\frac{1}{2}$  hour after the intravenous administration of the Se<sup>75</sup> methionine.

The patient received an early breakfast, consisting of 2 glasses of milk, I piece of toast and a cup of coffee (no sugar). Four hours after this meal, the patient received 30 cc. of whiskey by mouth. Scanning was performed 30 minutes later, using the 3 inch probe with the 3 inch broad focusing collimator. The patient was scanned from

above the xyphoid to the umbilicus in the supine position. Scanning time was about 45 minutes.

### RADIATION DOSIMETRY

Selenium 75 has a 120 day physical half life and based on estimates of a 100 day biological half life in the human has an effective half life of 56 days. The dose rate for the gamma emissions is 1.56 r/mc-hr. at 1 cm. distance. Based on investigations by Blau and Manske,² the liver retains 10

per cent of the administered dose for 1 day and the pancreas retains 7 per cent of the administered dose for 4 hours. If the dose administered is 210  $\mu$ c of Se<sup>75</sup> (3  $\mu$ c/kg. in a 70 kg. man), the total body integral dose would be in the order of 1.3 r, the liver integral dose .05 r and the pancreas integral dose .06 r.

### RESULTS

The scans were evaluated by 4 different observers and were divided into 4 catego-

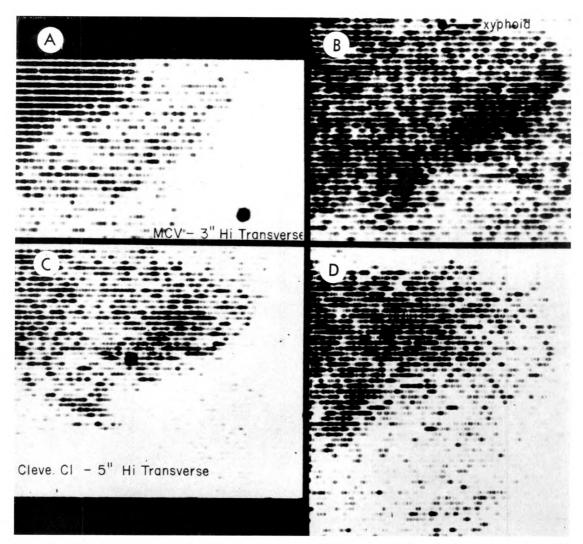


Fig. 4. (A-D) Representative scans of the pancreas of the high transverse morphology. In C the technique was used as described by Rodriguez-Antúnez<sup>6</sup> of the Cleveland Clinic. It was the best of our scans using a 5 inch crystal. In the other scans the technique as described in the text with a 3 inch crystal was used. All scans were made in the supine position.

ries: good, fair, poor and inadequate for interpretation. Of the 33 scans, 9 were considered good, 9 were fair, 8 were poor and 7 could not be interpreted.

Of the 26 scans that could be interpreted, it appeared that 3 distinct morphologic patterns of the pancreas were present. These were referred to as (1) high transverse, (2) horseshoe, and (3) sigmoid (Fig. 1).

Eleven were interpreted to be of the *high* transverse shape, 7 were horseshoe and 8 were sigmoid in shape. Few, if any, had the appearance of the textbook picture of a normal pancreas (see Fig. 2 through 6).

### DISCUSSION

Most important is the fact that the normal pancreas assumes different morphogic patterns. This organ may well be

dynamic and full of motion and may change shape as it functions. With one exception, we have not repeated scans in the same individuals. We believe, however, that the pancreas assumes different normal static shapes, as do other organs, such as the stomach, sigmoid colon, heart, etc. Normal variation appears to be the rule in the animal kingdom.

It is accepted that in Diagnostic Radiology great effort is expended by the student in interpreting normal structures on the film or fluoroscopic screen before the abnormal is discerned. We feel that some of the difficulty with interpreting pancreatic scans as reported in the literature lies not alone with the more or less imperfected technique, but also with the paucity of the study of the normal appearance of this or-

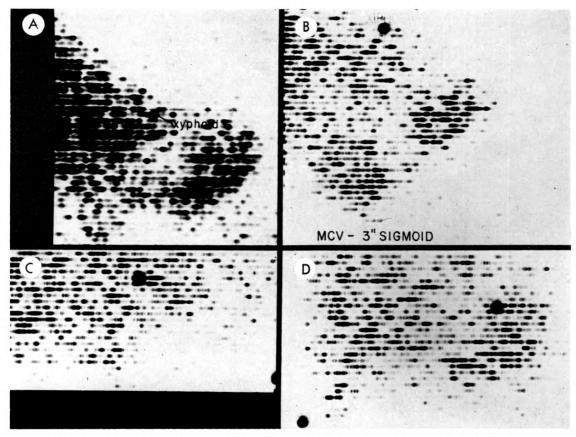


Fig. 5. (A-D) These scans show the *sigmoid* shaped pancreas in 4 patients. Notice gap areas. We chose not to use marks for what we believe to be the outline of the organ. These 4 patients were studied employing our technique as described in the text. The large dot represents the xyphoid process.

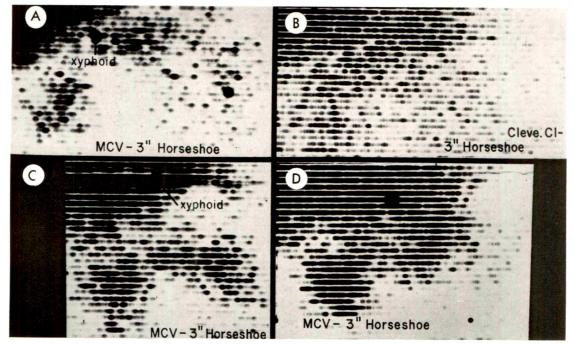


Fig. 6. (A-D) Pancreatic scans of the horseshoe shape. In B the technique of Rodriguez-Antúnez<sup>6</sup> of the Cleveland Clinic was used, while the technique as described in the text was used for the others. The large dot is the xyphoid process. Again notice the gap areas. These 4 patients, as well as all those cited in this article, had supposedly normal pancreases.

gan by most investigators. While it is not recommended that indiscriminate studies be made with radioisotopes in normal volunteers, such studies are at times indicated.

Many of our normal scans demonstrated areas which could be called space occupying. Many appeared abnormal in other respects. Perhaps no adult person has a "normal" pancreas. Possibly, the pancreas has a peristaltic activity as it expresses its exocrine secretions and these "gap" areas may represent peristaltic movements. If so, these movements must be extremely slow as about 45 minutes is required for scanning.

The authors feel that this breakthrough by Blau and his associates should continue to be evaluated and that biochemists and radiochemists should continue their efforts to produce a compound that by active biological localization can reveal the true appearance of this extremely important organ. E. Richard King, M.D. Department of Radiology Medical College of Virginia 1200 East Broad Street Richmond 19, Virginia

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### VALIDITY OF MEASURING REGIONAL PULMONARY ARTERIAL BLOOD FLOW WITH MACROAGGRE-GATES OF HUMAN SERUM ALBUMIN\*

By DONALD E. TOW, HENRY N. WAGNER, Jr., VINCENT LOPEZ-MAJANO, EDWARD M. SMITH, and TOHRU MIGITA

CINCE its introduction in 1931,7 pulmonary arteriography has been used to delineate the structure of the pulmonary vasculature. Advances in radioisotope technology have facilitated studies of the distribution of pulmonary arterial blood flow. Initially, Knipping and his associates<sup>14</sup> used the radioactive inert gas, xenon 133, to study ventilation. Others1,8,24 have extended the use of radioactive gases to study the regional distribution of pulmonary arterial blood flow in normal persons under different conditions and in patients with cardiopulmonary disease. More recently, a particulate distribution technique, using macroaggregates of human serum albumin labelled with a suitable gamma-emitting nuclide, has been used. This technique has been safe and effective in the diagnosis of pulmonary thromboembolism<sup>20</sup> and has recently been extended to study the distribution of pulmonary blood flow under various physiologic and pathologic conditions. The present report is concerned with the evidence for the validity of the method as a means of measuring the regional distribution of pulmonary arterial blood flow.

### THEORETIC BASIS

The particle distribution method is based on the principle of conservation of material. A known quantity (2) of indicator flowing into a region will be divided three ways: some ( $\mathcal{Q}_{\bullet}$ ) will accumulate in the region; some ( $\mathcal{Q}_{\bullet}$ ) will be metabolized; and the remainder ( $\mathcal{Q}_{\bullet}$ ) will flow out. The

total quantity  $\mathcal{Q} = \mathcal{Q}_i + \mathcal{Q}_m + \mathcal{Q}_i$ . The quantity  $(\mathcal{Q})$  is the product of the blood flow (F) and the concentration (C) in the blood vessels leading to the region. Therefore, the basic equation can be written as  $F \times C = \mathcal{Q}_i / \Delta t + \mathcal{Q}_m / \Delta t + \mathcal{Q}_o / \Delta t$ .

In the case of an ideal particle,  $\mathcal{Q}_{m}/\Delta t = 0$ and  $\mathcal{Q}_{s}/\Delta t = 0$ , that is, the material is not metabolized during the period of observation and all of it is accumulated in the region. Therefore, if the concentration (C) in the afferent vessels is uniform as a result of complete mixing, (2i) in any given region will be directly proportional to the regional blood flow. When  $(\mathfrak{D}_m)$  is not zero, the observation must be made before there has been a significant degree of metabolism, or the rate of degradation in various regions must be known. When (2,) is not zero, the method is still valid, provided there is insignificant recirculation of the labelled material.

### MACROAGGREGATES OF HUMAN SERUM ALBUMIN (MAA)

MAA labelled with either I<sup>131</sup> or Cr<sup>51</sup> has met most of the conditions necessary for the accurate measurement of regional pulmonary arterial blood flow. The size of the MAA particles is sufficiently large to result in their lodging in the pulmonary capillary bed in the first passage through the lungs. The metabolic degradation of the MAA as determined from the I<sup>131</sup> labelled material has a biologic half-time in the lungs of about 6 hours. With labelled human serum albumin of high specific activity, only 0.1

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<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965. Part of the symposium, "Critical Analysis of Some Diagnostic Tests Using Radioactive Isotopes." Chairman: Dr. Edith H. Quimby. From the Departments of Medicine and Radiology, The Johns Hopkins Medical Institutions, the Veterans Administration Hospital, Baltimore, Maryland and the Hospital for Special Surgery affiliated with the New York Hospital, Cornell Medical College, Department of Radiology.

to 0.5 ml. (equivalent to 0.1 to 0.5 mg. of albumin) is needed to provide statistically valid count rates.

### PREPARATION OF MACROAGGREGATED ALBUMIN

High specific activity (up to 3 mc of I<sup>131</sup> per mg.) human serum albumin is diluted in saline to make a 0.1 per cent solution, the pH of which is then adjusted to 5.5, the isoelectric point of the albumin. The solution is subsequently heated at 100° C. for 4 to 15 minutes in an oscillatory water bath at 100 cycles per minute. Sterile technique is maintained throughout the procedure. The final product is tested for sterility and pyrogenicity prior to administration to man. The particles settle on standing. Therefore, gentle shaking before withdrawal is necessary to ensure uniform distribution of the aggregates.

### PHYSICAL CHARACTERISTICS OF MAA

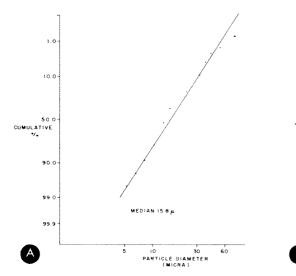
When examined undiluted under the light microscope, the preparation appears as conglomerates of aggregates assuming different shapes. The majority have a diameter in the order of  $50 \mu$ . When diluted in saline solution of pH 5.5, the conglomerates can be observed to break up and form an

uniform particle size approximately 10 to 15  $\mu$  in diameter. Whether in the diluted or the undiluted state, the aggregates can be seen to consist of the smaller units measuring approximately 10 to 15  $\mu$  in diameter and nearly spherical in shape.

To obtain an accurate estimate of the frequency distribution of the size of the MAA particles, the preparation was analyzed with a Coulter counter. Five mg. of the MAA was suspended in 50 ml. of saline at pH 5.5. One milligram was found to consist of approximately 250,000 aggregates of size 7.3  $\mu$  or larger. More than 85 per cent by weight of the protein was distributed in the particle range of 9.2  $\mu$  or greater. The frequency distribution of sizes did not follow a normal probability function but rather a log normal probability distribution.<sup>4</sup> A plot of the size frequency distribution is shown in Figure 1, A and B.

### BIOLOGIC BEHAVIOR

When injected intravenously, MAA becomes lodged in the pulmonary capillary bed in the first passage through the lungs. This results from their size relative to that of the pulmonary capillaries, estimated by Weibel<sup>23</sup> to have an average internal diameter of 8  $\mu$  (range 1 to 15  $\mu$ ). The rate of clear-



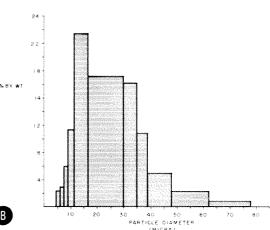


Fig. 1. Distribution of sizes of MAA particles. (A) Log cumulative per cent 25. log diameter of particle.
(B) Histogram of distribution of particle size by weight.

ance of the MAA from the lungs following injection is approximated by an exponential function. The values were obtained from normal subjects by means of an external radiation detector over the anterior chest following the injection of MAA into an antecubital vein.

### EXTRACTION EFFICIENCY

The distribution of various batches of the MAA was studied in rabbits and dogs. The procedure was as follows: 4 minutes after the intravenous injection of the MAA, the animals were sacrificed by injecting a saturated solution of MgSO<sub>4</sub>. At least 3 samples of approximately 1 gm. each were taken from each lobe of the lung and the radioactivity was measured in a well-type scintillation counter. The values average 77.2±15.1 per cent expressed as per cent of the administered dose in the lungs.

In man, the extraction efficiency was determined by continuous arterial sampling to detect the particles after intravenous injection. Brachial arterial blood was collected for I minute at a rate of I ml. per 4 seconds. Studies were performed on 5 volunteers and 4 patients with tuberculosis.

The radioactivity of heparinized whole blood was measured and the results were expressed as a percentage of the administered dose per liter of blood. Assuming an average cardiac output of 5 liters/minute, we calculated the extraction efficiency to be approximately 80 per cent, which is consistent with the direct measurement of the distribution in animals.

An extraction efficiency in the order of 80 per cent instead of the ideal 100 per cent does not introduce an appreciable error in the estimation of *regional* pulmonary arterial blood flow. Particles passing through the lungs are smaller aggregates of albumin (AA). They remain in the circulation until metabolized in the liver and spleen.<sup>18</sup>

### HEMODYNAMIC EFFECTS

Detailed studies of human lungs by Weibel<sup>28</sup> have shown that there are approxi-

mately 280 billion capillary segments. There are but about 250 thousand macroaggregates of size 7.3  $\mu$  or larger in diameter per mg. of protein. Furthermore, the pulmonary vasculature is a rich anastomotic network of capillaries. No elevation of pulmonary arterial pressure was observed in dogs until a dose of 10 mg./kg. was injected, compared to the usual dose in man which is not greater than 0.05 mg./kg.

#### BRONCHIAL CIRCULATION

Of the macroaggregates going through the lungs during the initial passage (20 per cent of the injected dose), only an insignificant amount reaches the lungs through the bronchial arterial vessels. In the absence of abnormal shunting of blood from the right to the left side of the circulation, most of the particles are delivered to the lungs via pulmonary arterial vessels, rather than bronchial vessels. Therefore, the regional flow, as measured by the MAA method, is only pulmonary arterial, rather than total flow.

### VARIABILITY OF DISTRIBUTION IN THE LUNGS

To ascertain whether mixing of the particles was uniform prior to their arrival at the lungs, variability of distribution of MAA was determined in animals. Dogs were sacrificed by intravenous injections of saturated solutions of MgSO<sub>4</sub> 4 minutes after intravenous injection of 300 to 500 µc of I<sup>181</sup> labelled MAA. Multiple samples of lung, approximately I gm. each, were taken from each lobe and the radioactivity was measured in a well-type scintillation detector. An average relative standard deviation of 20 per cent was observed, an indication that the particles had been uniformly mixed prior to distribution in various portions of the lungs. This degree of variability may be related to differences in composition of the samples or to differences in the distribution of pulmonary arterial blood flow associated with different positions of the lungs.

### RADIOAUTOGRAPHY

Sections of the lungs of dogs were studied by radioautography after fixation in formaldehyde. To optimize resolution, I<sup>125</sup> labelled MAA was used. Dogs were sacrificed 4 minutes after the intravenous injection of the labelled aggregates. Typical sections are shown in Figure 2, A and B. The aggregates can be seen distributed in the blood vessels of various sizes, arterioles and capillaries. When the sizes of MAA particles appearing in the sections of the lungs were compared with the *in vitro* distribution, it became apparent that the larger particles had fragmented before lodging in the smaller vessels.

### CORRELATION WITH THE DISTRIBUTION OF INJECTED RED BLOOD CELLS

In the use of a particulate indicator, such as MAA, to determine the distribution of

blood flow, one implicit requirement is that the distribution of the particles parallels that of the red blood cells. To study the distribution of red blood cells flowing into the lungs, the concept introduced by Sapirstein<sup>17</sup> was used. He proposed that regional blood flow could be measured from the distribution of an injected indicator, if the indicator could be detected as soon as it had arrived by way of the arterial blood flow but before it had passed through the region. MAA was labelled with I125 at a specific activity of 200 µc per ml. and red blood cells with Cr51 at 50 µc per ml. One-half of 1 ml. of each was mixed in the same syringe and injected intravenously into dogs. The animals were sacrificed by electric shocks across the chest 7 to 10 seconds after the injection. Thus, it was possible to determine the regional distribution in the lungs of the injected red blood cells. The lungs

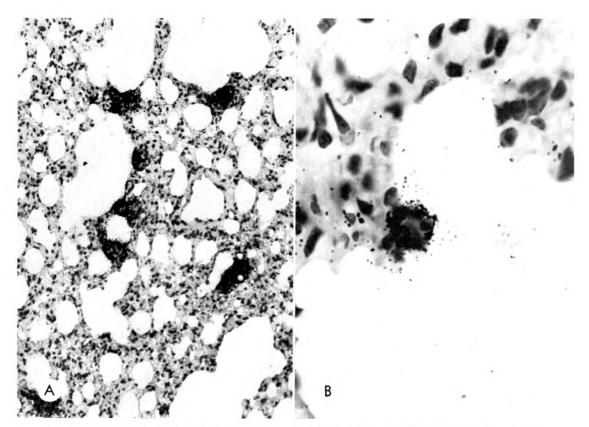


Fig. 2. (A and B) Radioautographs of section of lung tissue following injection of MAA, showing distribution of MAA particles.

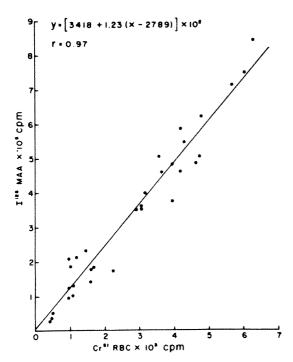


Fig. 3. Distribution of Cr<sup>5t</sup> labelled red blood cells and I<sup>125</sup> MAA injected simultaneously.

were removed carefully and frozen immediately to avoid displacement of blood. Three to 4 samples of approximately 1 gm. were obtained from each lobe while in the frozen state. The radioactivity was measured in a well-type detector using gamma ray spectrometry to measure I<sup>125</sup> and Cr<sup>51</sup>. The results in 2 animals are shown in Figure 3. The correlation coefficient was 0.97. It is evident that the distribution of MAA particles was linearly related to that of the red blood cells.

### QUANTIFICATION IN MAN

Quantification of the regional distribution of radioactivity in human subjects can be obtained by means of multiple stationary detectors or by a single detector moving in a predetermined pattern. The latter is simplest in design and operation. A single detection system with suitable collimator is adequate. A large crystal detector, because of its sensitivity, greatly decreases the time required to complete the scanning process.

Our subjects were lying supine during the

scanning procedure and were scanned with an 8 inch detector mounted beneath the subject and moving at a linear speed of 85 inches per minute. Data were recorded by two scalers, as well as photographically. In the photographic image, the pattern of distribution of radioactivity could be seen. Quantitative analysis of the regional distribution of radioactivity was accomplished in several ways.

One method was to count the number of dots printed during the scanning procedure. These are linearly related to the regional radioactivity. This method is tedious, since it is necessary to count a large number of dots closely placed.

The density of the film could also be used for quantification, provided the system was calibrated to correct for the response function of the film. The density of exposed roentgenographic film is a logarithmic function of the counting rate, except in the regions of very low or very high counting rates. Variation in film density observed in the lung scans of this report had a nearly linear relationship to the digital counting rate, as seen in Figure 4. A grid composed of 1.5×1.5 centimeter squares was used to determine the regional density of the lung scans.

Comparisons were made of different areas of the lungs or of the same area of the lung in different scans.

The data were also recorded by means of 2 separate scalers, one recording the activity in the left lung, the other in the right. Cumulative counts were recorded, usually from each 6 scanning lines corresponding to 2 cm. segments of the lung (Fig. 5). The radioactivity in particular segments of lung was expressed as a percentage of the total radioactivity in the lungs.

### CORRELATION WITH OXYGEN UPTAKE IN MAN

Differential spirometry is accepted as an estimate of the partition of pulmonary arterial blood flow between the 2 lungs in man.<sup>2</sup> The method is based on the principle that oxygen uptake is a direct function of the amount of pulmonary arterial blood

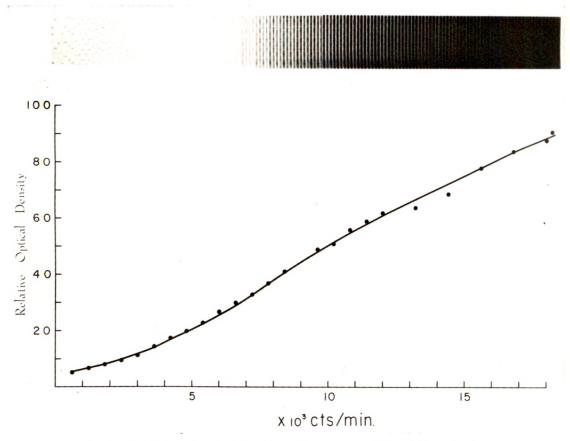


Fig. 4. Correlation of optical density of film and count rates, arithmetic plot.

flow to the area. Simultaneous measurements were made of the partition of pulmonary arterial blood flow between the 2 lungs as determined by the MAA technique and bronchospirometry. Details have been described elsewhere. 5,15 Briefly, 3 groups of patients with pulmonary tuberculosis were studied. Two groups of patients, consisting of 18 and 17 patients respectively, were studied at rest. A third group (10 patients) was studied during exercise. The oxygen uptake of each lung was measured by means of a Carlens catheter and expressed as a percentage of the total. In the first 2 groups, pulmonary scanning with MAA was performed from 3 to 10 days after the bronchospirometry; in the patients studied during exercise on a bicycle ergometer while supine, MAA was injected at the end of the fourth minute of exercise; bronchospirometry was performed simultaneously. Correlations between the scanning and bronchospirometry methods were excellent, correlation coefficients being 0.96, 0.98, and 0.95, respectively. Thus, the MAA technique of determining the regional distribution of pulmonary arterial blood flow was valid whether the subjects were at rest or during exercise when the cardiac output was increased to several times resting values.

## EFFECT OF POSTURE ON THE REGIONAL DISTRIBUTION OF PULMONARY ARTERIAL BLOOD FLOW

Gravity is an important factor in the regional distribution of the pulmonary arterial blood flow, because the pulmonary circulation is a low pressure system. The effect of the upright posture has been studied extensively. In order to evaluate the MAA technique, the effect of posture was studied in 6 subjects in the supine and sitting positions. The subjects were kept

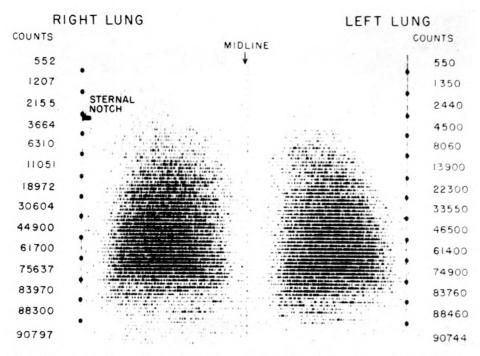


Fig. 5. Quantification of lung scans using 2 scalers. Cumulative counts from each lung are recorded segmentally.

as quietly as possible for 20 minutes in each posture before the injection of MAA. Lung scanning was performed in the supine position shortly after the injection. Segmental distribution of radioactivity was calculated as a percentage of the total of each lung. The lengths of the lungs were normalized into 10 equal segments for all subjects. In the supine position, the effect of gravity is uniformly distributed throughout the length of the lungs. Therefore, the distribution of pulmonary arterial blood flow in each segment was taken as unity in the supine position, and ratios of the regional distribution of pulmonary arterial blood flow in the sitting posture to the supine posture were calculated. The average values of the 6 subjects are shown in Figure 6, A and B, corresponding to the right and left lungs. In the uppermost segment of the right lung, blood flow during the sitting posture was 28 per cent of that in the supine position; in the left it was 44 per cent. The shift of blood flow was linear in both lungs until the lowest segment of the right and lowest 2 segments of the left lungs were reached.

# COMPARISON OF REGIONAL PULMONARY ARTERIAL BLOOD FLOW IN MAN DURING NORMAL BREATH AND BREATH HOLDING

It has been suggested that regional distribution of pulmonary arterial blood flow may be influenced by the phase of the respiratory cycle. Burton<sup>3</sup> concluded that negative pressure inflation of the lungs, as in normal inspiration, would lead to a decrease of the transmural pressure of the pulmonary arterial system. This would result in the shifting of pulmonary blood flow to the dependent parts of the lungs. In order to test the sensitivity of the MAA method, the pattern of regional pulmonary arterial blood flow was compared in 3 volunteers during normal breathing and at the height of inspiration. In both instances, the subjects were sitting upright when the MAA was injected. The ratio of the blood flow in each segment during full inspiration was compared to that during normal breathing by letting the blood flow of each segment during normal breathing equal to 1.0. The average values of the 3 subjects are shown in Figure 7, A and B. It is ap-

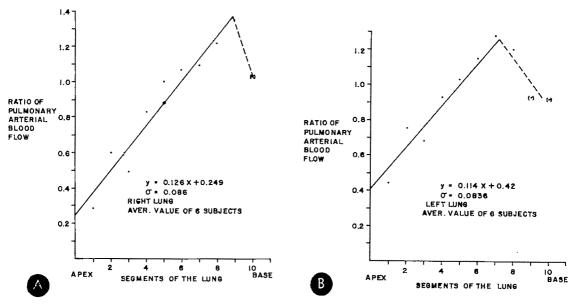


Fig. 6. Effect of erect posture on regional distribution of pulmonary arterial blood flow. Ordinate: ratio of blood flow in sitting posture to supine. (A) Right lung; (B) left lung.

parent that during full inspiration, pulmonary arterial blood flow was shifted downward, resulting in a decrease at the apex and an increase at the base. The change of the regional blood flow was linear until the lowest segment of the right and the lowest 2 segments of the left lung were reached. As in the previous postural studies, the significance of this deviation from linearity is not clear, although it is possible that these segments have higher vascular resistance due to their location below the level of the left atrium. The difference between the left and right lungs may be attributed to the fact that the left diaphragm is lower than the right.

### SAFETY AND DOSIMETRY

No hemodynamic or immunologic toxicity has been observed to date in more than 1,000 patient scans. Patients ranged in age from several months to 101 years, and had a variety of cardiopulmonary diseases.

### RADIATION ABSORBED DOSE

The following equations were used to calculate the absorbed dose:

$$\overline{D}_{\beta(\infty)} = 73.8 \overline{E}_{\beta} \sum_{j} Co_{j} T_{\bullet i t_{j}}$$
 (1)

$$\overline{D}_{\gamma(\infty)} = 73.8 \left[ \sum_{i} n_{i} E_{i} (AF)_{i} \right] \sum_{f} Co_{f} T_{\text{off}_{f}} \qquad (2)$$

$$\overline{D}_{\gamma(\infty)} = 0.0346\rho\Gamma\bar{g}CoT_{\rm eff} \tag{3}$$

where

 $\overline{E}_{\beta}$  = total local energy deposition per disentegration, mev./dist.

Co<sub>j</sub> = initial concentration of the MAA associated with the component of the uptake or disappearance curve for a given organ, μc/gm.

 $T_{\text{ett}_j}$  = effective half life of the jth component, days

 $N_i$ =number of photons with an energy  $E_i$ , mev.

 $(AF)_{i}$  = absorbed fraction

absorbed energy from a photon of energy  $E_i$ 

emitted energy from a photon of energy  $E_i$  $\rho$  = density of tissue under considera-

 $\rho$  = density of tissue under consideration, gm./cm.<sup>3</sup>

 $\Gamma$  = specific gamma-ray constant, rcm.  $^2$ /mc-hr.

 $\bar{g}$  = average geometric factor, cm.<sup>-1</sup>.

Equation I is the usual equation for calculating the beta component of the absorbed dose. The second equation utilizes the method developed by Ellett *et al.*<sup>9,10</sup> for calculating the gamma-component of

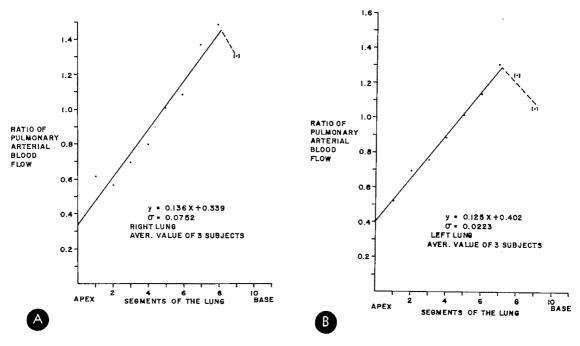


Fig. 7. Effect of full inspiration on regional distribution of pulmonary arterial blood flow. Ordinate: ratio of blood flow in full inspiration to normal breathing. (A) Right lung; (B) left lung. Subjects were sitting upright in both studies.

the absorbed dose. Equations 2 and 3 have been quantitatively compared by Smith. 18,19 Equation 3, introduced by Marinelli and Quimby, has been used to calculate the gamma component of the absorbed dose to the lungs since the other method has not been developed as yet for lung tissue.

### TOTAL BODY ABSORBED DOSE

The total body absorbed dose calculation was based on measurement of urinary and fecal excretion for a period of 30 days in 3 normal volunteers who had received I<sup>125</sup> MAA. The use of I<sup>125</sup> (t<sub>1</sub> physical 60 days) made possible the extended excretion studies necessary to account for all injected activity. A uniform distribution was assumed. Eighty-seven per cent of the  $I^{181}$  was excreted with a  $T_{\rm eff}$  of 0.47 day and the remainder with a  $T_{\rm eff}$  of 4.65 days. The absorbed fraction for a 70 kg. ellipsoidal phantom containing a uniform distribution of  $I^{181}$  is 0.136 and  $\overline{E}_{\beta}$  for  $I^{181}$  is 0.188 mev./dist. The total body absorbed dose is 0.1 rad, of which 60 mrads is due to the beta component and 40 mrads due

to the gamma component of the absorbed dose.

### BLOOD ABSORBED DOSE

The blood absorbed dose calculation was based on serial blood measurements made on 4 normal volunteers carried out for a period of 4 days. The initial concentration was  $0.013\pm0.005~\mu\text{c/gm}$ . of whole blood. The effective half life was 1.85 days. The beta component of the absorbed dose was  $0.33\pm0.07$  rads. This assumes that the total energy from the beta particles was absorbed in blood. The gamma component of the absorbed dose was taken to be equivalent to the gamma component of the total body absorbed dose, 0.04 rad.

### GONADAL ABSORBED DOSE

In males, the gamma component of the absorbed dose to the gonads is essentially the same as the gamma component of the total body absorbed dose; in females, the absorbed dose is about 5 per cent higher because of the position of the ovaries within the body. Evans *et al.*<sup>11</sup> demonstrated

that the ovaries do not concentrate iodide.

The beta component of the gonadal absorbed dose lies between the value for the total body and that for blood, depending upon blood flow to the gonads and the diameter and wall thickness of the blood vessels of the gonads. This results in a gonadal absorbed dose between O.I and O.4 rad.

### LIVER ABSORBED DOSE

The liver absorbed dose calculation was based on external counting over the liver in 7 normal volunteers for a period of 24 days who had received aggregated albumin. Approximately 20 per cent of the MAA went to the liver and spleen, and was assumed to be uniformly distributed. The liver was considered to be a 1.7 kg. flat ellipsoid. The absorbed fraction for a uniform distribution of I<sup>181</sup> in the liver is 0.057. The values for  $Co_j$  and  $T_{eff_j}$  are given in Table 1. The beta component of the absorbed dose is 0.26 rad and the gamma component is 0.08 rad.

### AVERAGE LUNG ABSORBED DOSE

The average lung absorbed dose calculation was based on external counting over the lungs of 9 normal individuals for a period of 4 days. It was assumed that 80 per cent of the MAA was trapped in the capillary bed of the lung and disappeared with an effective half-life of  $0.31 \pm 0.06$  day. There was a long lived component which consisted of approximately I per cent of the administered dose which was attributed to the I181 activity in blood. The lungs were assumed to weigh 1,000 gm. and to have a density of 0.3 gm./cm.8. The beta component of the absorbed dose was 0.97 ± 0.17 rads. The gamma component of the absorbed dose was calculated using equation 3. The value of g for a cylinder 24 cm. tall with a diameter of 10 cm. is 58 cm.<sup>-1</sup> and for a cylinder 24 cm. tall with a diameter of 20 cm. it is 93 cm.-1. The values of g are the revised values as calculated by Focht et al.12 The gamma component of the absorbed dose for two cyl-

Table I SUMMARY OF ABSORBED DOSE CALCULATION

	Initial Concentration, Co;*			Effective Half Life (days)			Absorbed Dose (rads)		
Organ	Coi	Co <sub>2</sub>	Co <sub>3</sub>	$T_{ m eff_1}$	$T_{{\sf eff_1}}$	Teff;	Beta Com- ponent	Gamma Com- ponent	Total
Total Body	c.8 <sub>7</sub>	0.13	_	0.47	4.65		0.06	0.04	0.1
Blood	0.013± 0.005 μc/gm.			1.85			0.33± 0.07	0.04	0.30-
Gonadal .				_			0.06-	0.04	0.1-
Liver	C.12	0.06	0.02	0.021	0.36	4.65	0.26	0.08	0.34
Average Lung	c.8o			0.31± 0.06			1.1-	0.11-	1.2-
Average Local Lung	0.80			0.31± 0.06			4.6- 6.6‡		

<sup>\*</sup> Fraction of administered dose unless otherwise noted.

<sup>†</sup> This includes the beta component of the absorbed dose to blood.

<sup>‡</sup> This includes only the beta component of the absorbed dose from the aggregates localized in the capillary beta.

inders is 0.09 r and for one cylinder 0.15 r. The difference is insignificant in the total absorbed dose because of the magnitude of the beta component. The long lived component of the total body gamma component of the absorbed dose was included in the average lung absorbed dose.

## AVERAGE LOCAL LUNG ABSORBED DOSE

A 0.2 mg. administered dose of MAA, density equal to 1.4 gm./cm.3, containing 300  $\mu$ c of I<sup>181</sup> with a mean diameter of 50 μ consists of about 2,160 spherical particles. As previously described, the 50  $\mu$ particles fragment after injection into approximately 10  $\mu$  particles. This results in 2.7×105 particles with an average activity of 1.1  $\times$  10<sup>-2</sup>  $\mu$ c. The surface area of the capillary bed of the lungs is approximately 70 m.2, and the average diameter of the capillaries is between 7 and 10  $\mu$ .<sup>23</sup> One can calculate a capillary volume of 173 cm.8 assuming that the capillary bed is a single hollow tube with a mean diameter of 10 µ and a surface area of 70 m.<sup>2</sup>. The capillary volume of 173 cm.8 is in good agreement with a lung blood volume of 300 ml.6 Assuming, then, that 80 per cent of the 10  $\mu$  particles are uniformly distributed in this 173 cm.3 volume and have an effective half life of  $0.31 \pm 0.06$  day, the average local beta absorbed dose to the epithelium would be 5.6±1.0 rads. This average absorbed dose is a realistic estimate of the local average absorbed dose over 95 per cent of the volume of a 1 mm.8 sphere if one considers that there are approximately 1.6, 10  $\mu$  particles per mm.<sup>2</sup> in the 173 cm.<sup>3</sup> capillary volume and the maximum range of the I<sup>131</sup> beta particles is approximately 2 mm. with an average range of approximately 0.6 mm.

## LOCAL LUNG ABSORBED DOSE

To calculate the local absorbed dose from a single MAA particle in the lungs is exceedingly difficult using the currently available point source beta absorbed dose equations because of the broad variation of tissue densities in the lungs. However, it is clear that the radiation received by the capillary epithelium adjacent to the particle is of several orders of magnitude greater than the *average* local dose.

## ADVANTAGES OF THE MAA METHOD

The application of the MAA method to the diagnosis of pulmonary thromboembolism, the study of the natural history of this disease in man, the evaluation of thrombolytic agents such as urokinase and the early diagnosis of the cancer of the lungs have been previously described. 20,21 More recently, lung scanning has been used to study the pattern of pulmonary arterial blood flow in patients with chronic pulmonary tuberculosis.16 An example of the use of lung scanning to detect marked asymmetric pulmonary blood flow in a patient originally believed to have diffuse bilateral emphysema is shown in Figure 8, A and B. The patient was a 62 year old male who had chronic asthma with dyspnea on mild exertion. The lung scan showed decreased perfusion of the right lung, although the chest roentgenogram did not show any difference between the 2

The lung scanning technique has also been applied to physiologic studies, such as the demonstration of the local effect of vasomotor agents injected into a branch of the pulmonary artery through a cardiac catheter.<sup>22</sup>

With our present scanning system, the resolution is  $\frac{1}{2}$  of an inch at the focal point of the collimator. Further improvement can be obtained by means of a better collimator, used together with low energy gammaemitting nuclides. With such nuclides as  $Tc^{99m}$ , which has no beta emission, one obtains better resolution as well as lower radiation dose to the patient. Figure 9 is the lung scan of a dog using  $Tc^{99m}$  labelled macro-aggregated albumin.

An important advantage of the MAA method is that we need only to inject the particles intravenously under the physiologic or pathologic condition that we wish to study. The scanning procedure may be

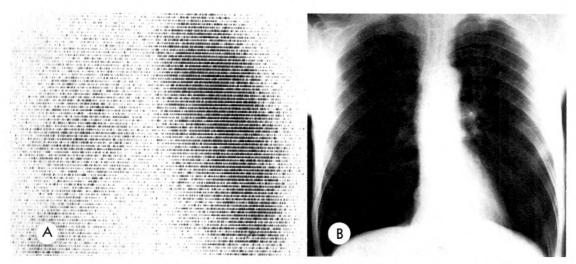


Fig. 8. (A) Lung scan of a patient with chronic asthma and dyspnea on exertion. (B) Chest roentgenogram of same patient.

delayed as long as 3 to 4 hours, since the scanning pattern does not change over that period of time. An example of the versatility of the method is the study carried out in collaboration with Warren and Stone of the School of Aerospace Medicine of the U. S. Air Force. The objective was to determine the effect of zero gravity on regional pulmonary blood flow. The first step was to determine the distribution of regional blood flow in 6 fliers scanned immediately and 1½ hours after the injection of MAA. The difference in the relative dis-

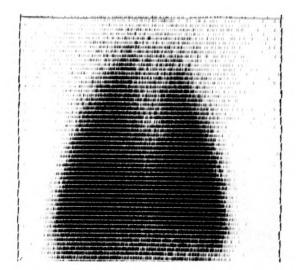


Fig. 9. Tc99m labelled MAA lung scan of a dog.

tribution of particles throughout the lungs was not significant. In the second phase, MAA was injected in each subject when he was subjected to zero gravity during parabolic flight. Lung scanning was performed 1½ hours later.

The preparation of MAA is simple and inexpensive. The particles are readily metabolizable and the procedure may be repeated daily if necessary.

## SUMMARY

Evidence for the validity of the MAA method in the determination of regional pulmonary arterial blood flow is: (a) sizes of the particles are optimal; (b) extraction efficiency is high; (c) uniform mixing of the particles is complete prior to their arrival at the lungs; (d) the distribution of the macroaggregates and the red blood cells is similar; (e) correlation with differential spirometry in man at rest and during exercise is good; and (f) the known effects of erect posture and phasic variation of the respiratory cycle on the pattern of distribution of pulmonary blood flow in man were clearly demonstrated.

Donald E. Tow, M.D. Department of Radiological Science The Johns Hopkins Medical Institutions 615 N. Wolfe Street Baltimore, Maryland 21205 We are grateful to Dr. R. Northcutt of the United States Naval Hospital, Bethesda, Maryland, for his assistance in the preparation of the radioautography; to Dr. S. Permutt of the Department of Environmental Medicine for his advice on the analysis of the postural data; to Mr. C. V. Smith, Jr., of the Department of Radiological Science of the Johns Hopkins Medical Institutions, for his advice on the spectral analysis of the MAA particles; and to our laboratory staff for their technical assistance.

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## PLACENTAL LOCALIZATION WITH RADIOISOTOPES\*

## RESULTS IN 86 VERIFIED CASES

By PHILIP M. JOHNSON, M.D., JOHN J. SCIARRA, M.D., and DAVID G. BRAGG, M.D. NEW YORK, NEW YORK

NE index of the clinical importance attached to localization of the placenta is the number and variety of techniques available for the purpose. When the position of the placenta is known, the differential diagnosis of antepartum vaginal bleeding is simplified or solved. Correct management of the bleeding gravid patient requires knowledge of whether abnormally low placentation—placenta previa—is present.

Roentgenographic methods of placental localization have been employed since 1930. They may be classified as indirect or direct. The most widely used indirect method is soft tissue placentography, in which the position of the placenta may be deduced by the effect of the placental mass upon adjacent structures. Aortography and selective retrograde arteriography are direct methods that opacify the maternal intraplacental circulation, thus allowing visualization of placental size and position. Although more accurate than indirect placentography, these techniques are more difficult and carry the risks of bleeding and formation of hematoma at the arterial puncture site.

The application of radioactive tracers for placental localization was first reported in 1950 by Browne and Veall.¹ Using Na²⁴Cl, these investigators identified the position of the placenta in 50 patients and described the basic criteria for interpretation of data. However, radioisotope placentography received little clinical acceptance until 1957 when the successful use of a more satisfactory radiopharmaceutical, I¹³¹-labeled human serum albumin (HSA), was reported by Weinberg and colleagues.¹ Since then, radioisotope placentography has become

widely employed in the investigation of third trimester bleeding and for other purposes. Refinements have resulted from technical improvements and the introduction of additional radiopharmaceuticals. The latter include I<sup>132</sup>-labeled HSA,<sup>2</sup> Cr<sup>51</sup>-labeled red cells,<sup>5</sup> Cr<sup>51</sup>-labeled HSA,<sup>3</sup> and HSA labeled with Tc<sup>99m</sup>.<sup>4</sup>

In many centers radioisotope placentography has superseded roentgenographic placentography. There are 2 reasons for this change. First, placental localization with radioisotopes is more accurate. Thaidigsman and Schulman6 have recently reported a comparison of both methods in a single group of patients. The placental site was correctly predicted by indirect roentgenographic placentography in 78 per cent of cases and by radioisotope placentography in 91 per cent. Second, the amount of radiation delivered to mother and fetus by any form of roentgenographic placentography is many times greater than that resulting from current radiopharmaceutical techniques.

This report is an analysis of the results and accuracy of radioisotope placentography at the Columbia-Presbyterian Medical Center based on a review of 86 cases in which the anatomic site of placentation was subsequently verified.

## MATERIALS AND METHODS

Table I shows the number of patients examined according to duration of pregnancy and presence or absence of vaginal bleeding. Patients were referred for placental localization for I of 4 indications: vaginal bleeding, impending amniocentesis or intrauterine transfusion, suspicion of fetal death and evaluation of Cr<sup>51</sup> HSA as an

<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965. Part of the symposium, "Critical Analysis of Some Diagnostic Tests Using Radioactive Isotopes." Chairman: Dr. Edith H. Quimby. From the Departments of Radiology and Obstetrics & Gynecology, Presbyterian Hospital, New York, New York.

TABLE I

TABULATION OF PATIENTS UNDERGOING RADIOISOTOPE PLACENTOGRAPHY BY CLINICAL STATUS
AND BY RADIOPHARMACEUTICAL ADMINISTERED

Tri-	Patients		nts with Bleeding	HSA* Labeled		
mester	Ex- amined	Total	Placenta Previa	Lin	Cr <sup>51</sup>	
2nd	4	İ	I	2	2	
3rd	82	34	13	47	35	
Total	86	35	14	49	37	

<sup>\*</sup> HSA = human serum albumin.

agent for placentography. Patients in the last category were scheduled for secondary cesarean section.

Placental localization was begun 10 minutes after intravenous injection of 5  $\mu$ c of I<sup>131</sup> HSA or 35 μc of Cr<sup>51</sup> HSA. Patients receiving I181 were given Lugol's solution, 10 drops 3 times daily for 3 days beginning 24 hours before localization when possible. The net count rate (cpm) was measured at the precordium and at 14 points on the anterior abdominal wall and both flanks. The upper row of counting points lay at the superior margin of the uterine fundus as determined by palpation. On completion and after voiding, measurements of radioactivity at the precordium and at the lowest counting point (the pubic symphysis) were repeated.

Instrumentation consisted of a 2 inch sodium iodide (Th) crystal with 1½ inch lead shielding recessed 3 inches within a flat field collimator having an internal diameter of 3 inches at its face. Counting time at each point was 30 seconds. Counts were recorded on a decade scaler without spectrometry.

The method of data display and analysis was similar to that described by others. The net count rate at each point counted was expressed as a per cent of the precordial count rate, which was arbitrarily assigned a value of 100 per cent. By inspection of the pattern of count rate distribution, the area

of maximal abdominal radioactivity was noted. This was considered to correspond to the placental site. The position of the placenta was then described in vertical, transverse and sagittal planes.

The anatomic placental site was later determined in each patient. The method of verification was manual removal of the placenta at cesarean section (in 57 patients), manual removal at vaginal delivery (16 patients), inspection at hysterotomy (4 patients), unequivocal roentgenographic placentography followed by normal vaginal delivery (2 patients), and amniography and multiple bloody amniocenteses (I patient each). In 5 additional patients, of whom 4 presented with late third trimester bleeding, the vertical position of the placenta was determined by sterile pelvic examination. The absence of palpable placental tissue and the subsequent normal vaginal delivery of these patients excluded the possibility of placenta previa. The placental site was recorded as "fundus" in these patients.

## RESULTS

Comparison of the predicted versus the actual placental location disclosed agreement in 83 of the 86 patients examined. The accuracy of radioisotope placentography was therefore 96.4 per cent (Fig. 1).

In 71 patients the placenta lay in the fundus; this site was predicted in all 71. In I patient, a 39 year old multipara examined in the 32nd week of gestation for vaginal bleeding, a prediction of enlarged placenta with previa was made, based on high count rates at all abdominal points (Fig. 2). At hysterectomy, 4 weeks later, the uterus was term-sized and filled with clear, grape-like vesicles. The uterus and contents weighed 2,250 gm. Pathologic diagnosis was hydatidiform mole, potentially malignant. For the purposes of this analysis, the true placental location was considered fundus and the case is listed as a diagnostic error. We are not aware of previous descriptions of the findings at radioisotope placentography in placental neoplastic states.

In 14 patients with partial or total placenta previa, the correct location was predicted in 12. In 2 patients the presence of placenta previa was not detected. In both cases the previa was partial and the bulk of the placenta lay posteriorly. In 1 patient the presence of a 4 cm. fibroid on the posterior uterine wall may have contributed to an erroneous preciction of "subfundus" placental site. In the second patient an unexplained high count rate in the fundus was misinterpreted as the placental site despite an elevated count rate at the pubic symphysis.

## DISCUSSION

The accuracy of radioisotope placental localization in this series compares favorably with that reported by others. Both of the radiopharmaceuticals (I<sup>131</sup> HSA was given to 49 patients and Cr<sup>51</sup> HSA to 37 patients) proved satisfactory. Count rates at the precordium were 5,000 counts per minute or higher. Although the administered dose of Cr<sup>51</sup> HSA was 7 times that of I<sup>131</sup> HSA, the calculated radiation dose de-

# RESULTS OF LOCALIZATION IN 86 VERIFIED CASES

(OVERALL ACCURACY 96.4%)

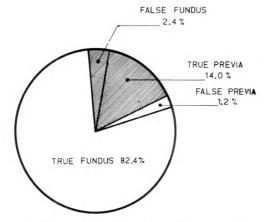


Fig. 1. Analysis of accuracy of placental localization in this series. Hatched segments represent propertion of patients with placenta previa.

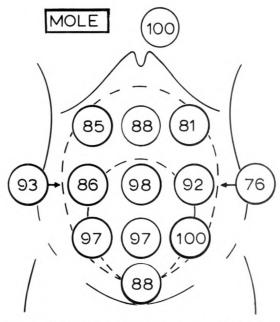


Fig. 2. Abdominal radioactivity pattern obtained at radioisotope placentography in a patient with hydatidiform mole (P.H. #1622292). See text for details.

livered to fetal and maternal blood and whole body was virtually identical for both agents.<sup>3</sup> The lack of  $\beta$  emission by  $Cr^{51}$  is the chief reason for the favorable radiation dosimetry of this nuclide. The larger administered dose is required to offset the relatively infrequent (9 per cent) emission of the detectable 323 kev. gamma ray. Since  $Cr^{51}$  does not undergo concentration in thyroid tissue, premedication with saturated potassium iodide solution is not necessary.  $Cr^{51}$  HSA is considered superior to  $I^{131}$  HSA for placental localization.

Radioisotope placentography is well tolerated by the patient, requiring a single intravenous injection. Its accuracy in predicting the placental site is very high. However, accuracy is lower in the presence of partial posterior placenta previa, as noted above and reported by others. Radioisotope placentography is superior to roentgenographic placental localization because of higher accuracy and lower radiation dose. The possibility of placenta previa must be evaluated in the differential diagnosis of the third trimester patient with vaginal bleed-

ing or persistent abnormal fetal presentation in order for proper obstetrical management to be instituted. Radioisotope placentography is, at present, the safest and simplest method for such evaluation. It seems assured of further refinement in accuracy and in detection of abnormal placental morphology by the recent introduction of placental scanning with Tc<sup>99m</sup>.<sup>4</sup>

## SUMMARY

The accuracy of radioisotope placentography in predicting placental location was 96.4 per cent in a group of 86 patients in whom anatomic verification of the placental site was obtained. Both I<sup>181</sup>-labeled human serum albumin and Cr<sup>51</sup>-labeled human serum albumin were employed in this series. Cr<sup>51</sup> human serum albumin was considered the superior radiopharmaceutical since no premedication was required. Radioisotope placentography is the method of choice for evaluating the possibility of placenta previa.

Philip M. Johnson, M.D. Presbyterian Hospital 622 W. 168th Street New York, New York 10032 Sterile radiochromated human serum albumin (Cr<sup>51</sup> HSA) was kindly supplied by Dr. Gordon Lindenblad, E. R. Squibb & Sons, Inc., New Brunswick, N. J.

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## PLACENTAL LOCALIZATION: A COMPARISON OF RADIOPHARMACEUTIC AND THERMOGRAPHIC METHODS\*

By PHILIP M. JOHNSON, M.D., DAVID G. BRAGG, M.D., and JOHN J. SCIARRA, M.D. NEW YORK, NEW YORK

IN THE differential diagnosis of third trimester bleeding, a number of established techniques is available to determine the position of the placenta. Excepting sterile vaginal examination, methods of placental localization are roentgenologic or radiopharmaceutic in nature and inevitably require exposure of mother and fetus to ionizing radiation. Radiopharmaceutic placentography has gained wide acceptance due to its accuracy (of the order of 90 per cent or higher) and the low associated radiation exposure.10,15-18

Recently, there was introduced a qualitatively distinct method of placentography not requiring the use of ionizing radiation.3 Its rationale rests on the fact that the placenta, or any large circulating blood pool, tends to elevate the temperature of the adjacent body surface. Thermometry of large body areas became clinically feasible with the development of the infrared recording camera, by which the surface temperature of the abdomen or the entire body can be rapidly and accurately quantitated. Since the intensity of infrared radiation per unit surface area of a "black body" is proportional to that area's warmth, the temperature of such a surface can be determined if its infrared emissivity is known. In 1934, Hardy<sup>8</sup> demonstrated that human skin is, in thermal terms, a "black body" having an infrared emissivity value of 99-100 per cent.

Lawson<sup>18</sup> first produced a workable thermal reproduction in 1956 by recording infrared emission with an evapograph. The prototype of the currently available infrared thermal scanner was described by

Astheimer and Wormser in 1959. The thermograph, which has been described in detail,<sup>2</sup> consists basically of a thermistor to convert focussed incident infrared radiation into a pulsed signal, a glow tube that emits visible light in proportion to the incoming signal, a Polaroid camera, and an automatic scanning device. The instrument is said to record 60,000 discrete thermal measurements within a field measuring 10 by 20 angular degrees. Its resolution is high and it is sensitive to temperature variations of as little as 0.1° C. With this instrument, infrared thermography is currently being applied to the investigation of peripheral vascular disease, arthritis and burns, and to the detection of neoplasms of the female mammary gland, the central nervous system, and other organs. 5,6,9,19 Thermography has proved valuable in the diagnosis of occlusion of the internal carotid artery.<sup>20</sup>

If thermoplacentography is as accurate andreliable as radiopharmaceutic placentography, it would, by its avoidance of fetomaternal irradiation, become the preferred method of placental localization. Accordingly, a clinical evaluation of thermoplacentography was undertaken.

## SUBJECTS AND METHODS

During a recent 9 month period, all patients referred for placental localization underwent both radiopharmaceutic and thermographic placentography (paired localization). Many patients had unexplained third trimester bleeding and were being evaluated for the presence of a placenta previa. Some patients had placentography for other reasons, i.e., pre-amniocentesis, etc. Our technique of radioplacentography

From the Departments of Radiology and Obstetrics & Gynecology, Columbia University College of Physicians and Surgeons and The Presbyterian Hospital, New York, New York.

<sup>\*</sup> Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October

has been described;<sup>11</sup> the radioactive tracer employed was human serum albumin labeled with  $Cr^{51}$  or  $I^{181}$  in intravenous doses of 35  $\mu$ c and 5  $\mu$ c, respectively. Strong iodine solution was administered orally to patients receiving the latter nuclide.

Upon completion of radiopharmaceutic localization, the patient was placed supine on a padded stretcher in the thermography room. This was a large interior windowless chamber in which the ambient temperature was maintained at 68°-70° F. by a forced air system. The patient lay quietly with abdomen unclothed for 15 minutes before thermography was begun. There was at no time evidence of significant fluctuation of room temperature during clinical thermography.

When the scanning area had been delineated, the response of the thermograph was adjusted to encompass the abdominal temperature range as determined by preliminary hand scanning with an infrared thermometer. The position of the umbilicus was often marked with a small object of low infrared emissivity such as an ordinary paper clip. Thermal scanning of the abdomen required about 15 minutes; the thermogram was ready for viewing 10 seconds after completion of the procedure.

Interpretation of the radioplacentograms was in accordance with standard methods. 11 The thermal placentograms were interpreted by visual inspection, analogous to the "reading" of diagnostic roentgenograms. A thermoplacentogram displays gradations of density from white to black with intermediate gray tones. Blackness indicates temperatures below the lowest abdominal skin temperature and whiteness corresponds to temperatures greater than the highest abdominal skin temperature. Laterality is reversed by the optical system of the instrument.

The anteriorly situated placenta was sought as a well-defined white ovoid or rounded area ("warm spot") within the confines of the surface projection of the uterus. The vertical position of this area relative to the pubic symphysis was then determined. Extension of the "warm spot"

into the suprapubic region was considered indicative of a low-lying anterior placenta, and limitation of the warm area to the suprapubic region was considered evidence of a placenta previa. When there was a less intense "warm spot" or when localized warmth was observed close to the lateral abdominal wall with no central "warm spot," the placenta was considered to lie posteriorly. When the temperature of the abdomen was relatively uniform or warm areas appeared inappropriately small, ill-defined, or continuous with extrauterine warm areas, the placental site was considered unidentified.

The analysis reported here was restricted to those patients in whom technically satisfactory paired localizations were available and in whom the placental site had been verified by manual removal of the placenta or by other methods. All thermoplacentograms were reviewed by 2 of the authors without knowledge of the original interpretation, the true placental site or the result of the radioplacentogram. The final thermographic interpretation represented a consensus under as fully objective conditions as possible. The same precautions were employed in reviewing the radioplacentograms.

## RESULTS

Paired radiopharmaceutic and thermal placentography was performed in more than 100 patients. The true placental site was subsequently determined in 44 of those patients in whom satisfactory paired localizations had been recorded. Certain characteristics of this group are as follows: mean age, 29.5 years (range 17–41 years), mean gestational age at examination, 36.2 weeks (range 20–40 weeks), mean number of pregnancies and previous deliveries, 3.6 and 1.9, respectively. The gestational age in 11 patients was 35 weeks or less.

The placental site was determined by manual removal of the placenta at cesarean section (32 patients), manual removal following vaginal delivery (7 patients) and visualization at hysterotomy or by amniography (1 patient each). In 3 patients the true site was not positively identified. However,

Table I

OVER-ALL RESULTS OF THERMOPLACENTOGRAPHY

Placental	Number	Vertical Thermographic Localization			
Implantation Site		Correct	Incorrect	None 12	
Fundus	32	18	2		
Posterior	15	8	2	5	
Anterior	13	8	0	5	
Not Further Described	4	2	0	2	
Subfundus	7	3	0	4	
Posterior	I	0	0	I	
Anterior	6	3	0	3	
Previa	5	I	4	0	
Total	2	I	I	0	
Marginal	3	0	3	0	
Totals	44	22	6	16	

the absence of palpable placental tissue on sterile vaginal examination and the subsequent normal vaginal delivery of each patient justified exclusion of the possibility of placenta previa and classification of the placental site as probably fundal.

The vertical position of the placenta was correctly predicted by the radiopharmaceutic method in 43 of the 44 patients. An erroneous prediction of a fundal site was made

in I patient in whom a partial posterolateral placental previa was present.

Thermoplacentography resulted in correct vertical localization of the placenta in 22 patients, incorrect localization in 6 patients and nonlocalization in 16 patients (Table 1). A fundal placental site was present in 32 patients and was identified thermographically in 18 (Fig. 1, A and B). A subfundal (midcorpus) site was present in 7 and

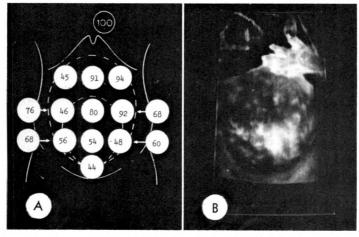


Fig. 1. Left anterior fundal placental site: 37th week of gestation. (A) Radioplacentogram. High count rates in fundus, expressed numerically as per cent of precordial count rate (black circle), indicate placental site correctly. (B) Thermoplacentogram demonstrates placental "warm spot" anteriorly but suggests a subfundal (mid-corpus) site. Well-defined black (cool) crescent in suprapubic area permits exclusion of marginal placenta previa. Note: patient's right side is on left side of A and right side of B in this and subsequent figures.

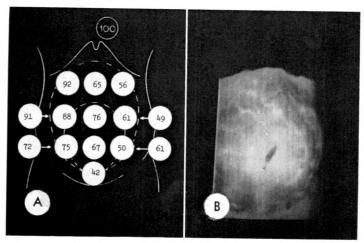


Fig. 2. Anterior fundal-subfundal site: 34th week of gestation. Both radioplacentogram (A) and thermoplacentogram (B) correctly indicate an anterior placental site above lower uterine segment. Subfundal extension of placenta is shown thermographically.

demonstrated in 3 (Fig. 2, A and B). Of the 19 sites known to be anterior in the fundus or subfundus, 11 were demonstrated, while of 16 posterior sites above the lower uterine segment, 8 were identified. Placenta previa was correctly determined in 1 of 5 patients (Fig. 3, A and B). None of the 3 marginal placenta previas was correctly predicted (Fig. 4, A and B); and 1 of 2 total placental previas was not discovered thermographically (Fig. 5, A and B). In 3 of the cases of placenta previa, the thermographic pre-

diction was a posterior fundal site.

An analysis of the 6 patients in whom an incorrect placental site was predicted thermographically is given in Table II. Three of these patients were examined 5 or more weeks from term. Of the 6 patients incorrectly localized, 4 had placenta previa, which was marginal in 3 cases. In the 16 patients in whom the placenta was not identified thermographically (Fig. 6, A and B; and 7, A and B; Table III), there was no evidence that placental position or gesta-

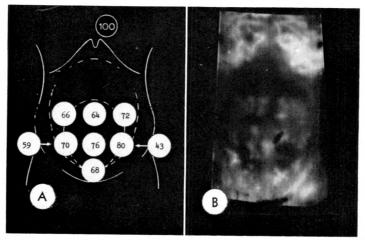


Fig. 3. Total placenta previa: 20th week of gestation. (A) Radioplacentogram discloses abnormally elevated count rates over lower uterine segment, indicative of placenta previa. (B) Thermoplacentogram shows maximum warmth throughout suprapubic area, consistent with placenta previa. However, compare with Figure 8B.

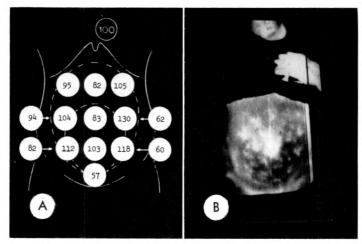


Fig. 4. Marginal placenta previa, right posterolateral: 36th week of gestation. Abnormal placental site is indicated by radioplacentography (A) but not by thermoplacentography (B) which suggests left-sided fundal-subfundal site.

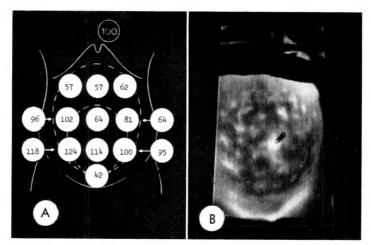


Fig. 5. Total placenta previa: 40th week of gestation. Radioplacentogram (A) indicates placenta previa, although not permitting diagnosis of total previa. Thermoplacentogram (B) does not clearly delineate placental site despite evidence of slightly increased suprapubic warmth. (Compare with Figure 6B.)

TABLE II
THERMOPLACENTOGRAPHIC LOCALIZATION ERRORS

Case No.	Age Race	Gravida/Para	Weeks Gravid at Examination	Predicted Site	True Site
23	31 N	3/2	36	Fundus posterior	Marginal previa posterior
26	33 W	3/2	29	Fundus posterior	Marginal previa anterior
33	33 W	4/3	35	Subfundus anterior, ? previa	Fundus posterior
52	19 W	3/2	39	? previa anterior	Fundus posterior
60	23 W	3/1	40	Fundus posterior	Total previa
67*	31 N	2/0	30	Fundus anterior	Marginal previa posterior

<sup>\*</sup> Also incorrectly localized by radiopharmaceutic method.

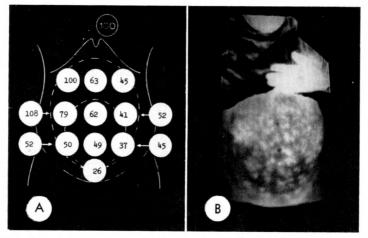


Fig. 6. Right anterolateral fundal site: 39th week of gestation. Radioplacentogram (A) unequivocally demonstrates site, but thermoplacentogram (B) does not localize placenta. Note increased warmth in suprapubic region.

tional age were significant factors. The difficulties inherent in thermographic recognition of the placental site and in differentiation of placental and nonplacental "warm spots" (Fig. 8, A and B) are indicated by the number of cases in which the placenta was not identifiable.

## DISCUSSION

Birnbaum and Kliot<sup>4</sup> have reported successful thermographic placental localization in 51 of 53 patients. Verification of placental site was by palpation after vaginal delivery in all but 8 patients. These investigators state that although anterior *versus* posterior

localization is imprecise, vertical localization is quite definite and that "significant placenta previa" can be excluded. Their data do not, however, list the number of cases of placenta previa examined thermographically. Haberman, Brueschke and Gershon-Cohen<sup>7</sup> have reported accurate thermographic placental localization in 48 of 54 patients, including 2 with placenta previa. The actual placental site was determined by roentgen placentography in 11 patients and by manual exploration of the uterus in 37. The 6 localization errors occurred in the presence of a posterior placental site.

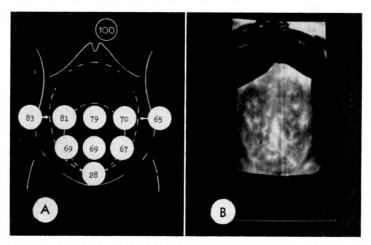


Fig. 7. Right anterior fundal site: 23rd week of gestation. Radioplacentogram (A) correctly indicates placental site not localized on thermoplacentogram (B).

Table III
NONIDENTIFICATION OF SITE BY THERMOPLACENTOGRAPHY

Case No.	Age Race	Gravida/Para	Weeks Gravid at Examination	True Placental Site
29	34 N	2/1	39	Fundus posterior
31	36 W	3/1	39	Fundus anterior
35	32 W	3/2	23	Fundus anterior
40	25 W	2/1	40	Fundus anterior
41	27 W	2/1	30	Subfundus posterior
42	34 N	1/0	40	Fundus posterior
47	27 N	3/2	40	Subfundus anterior
48	28 N	8/2	39	Fundus posterior
51	34 N	2/1	39	Fundus posterior
53	25 W	2/I	39	Subfundus anterior
57	29 W	3/2	39	Fundus anterior
61	31 W	5/3	40	Fundus posterior
62	39 N	7/3	38	Fundus anterior
66	27 W	4/I	22	Subfundus anterior
83	36 W	5/2	36	Fundus*
91	26 N	3/2	37	Fundus*

<sup>\*</sup> Site not further described.

In our group of 44 patients, the true placental site was determined by visual inspection and manual removal of the placenta at cesarean section in 32, and by potentially less reliable methods in 12. The accuracy of thermographic localization of

the placental site was precisely 50 per cent. The site was incorrectly identified in 16 per cent and could not be identified in 34 per cent of patients. The experience in 5 patients with placenta previa was unsatisfactory, the abnormal placental site having

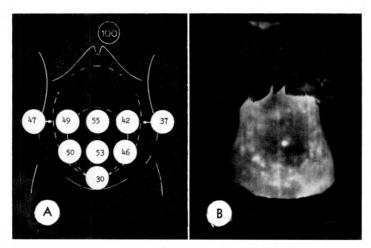


Fig. 8. Fetal demise: 20th week of gestation, fetal death 4 weeks earlier. Radioplacentogram (A) does not disclose placental site, indicating occlusion of placental circulation. Increased suprapubic warmth shown by thermoplacentogram (B) incorrectly suggests placenta previa. Placental site lay in anterior fundus at subsequent abortion.



Fig. 9. Placental scan employing Tc<sup>99m</sup>-labeled albumin (1.0 mc intravenously) completed in 20 minutes and demonstrating the placenta high in the left wall of the uterine fundus (arrows).

been detected thermographically in only 1 case. Accuracy of thermoplacentography was not increased by excluding the 11 patients examined prior to the 36th week of gestation. The procedure was most inaccurate in the presence of marginal placenta previa associated with early gestational age.

It is open to question whether objective quantitation of thermal data or construction of isotherm lines would increase the accuracy of localization, and a decision in this regard must await the undertaking. Until means are found to raise its accuracy, thermoplacentography must be regarded as having limited clinical utility at this time. If the thermogram clearly demonstrates the placental "warm spot" at a site well removed vertically from the symphysis, the probability is high that the placenta lies anteriorly in the fundus. In our series, no anteriorly situated placenta was incorrectly localized although 8 were not identified. However, if thermoplacentography is inconclusive or suggests an abnormal placental site, it should become the responsibility of the examiner to recommend radioplacentography or one of the more advanced roentgenographic methods for further evaluation.

Thermoplacentography has several clinical advantages, including avoidance of radiation to the fetus and mother and derivation of positional and morphologic information. Its disadvantages include expense, the need for separate physical facilities, and the introduction of thermographic artefacts from motion of the patient, especially during the discomfort of uterine contractions. Additional studies will further define the clinical utility of thermoplacentography. The accuracy of placental site verification is obviously critical, and methods such as soft tissue roentgen placentography, palpation of the placental site per vaginam, etc., must be considered less reliable for purposes of evaluation than manual removal of the placenta at cesarean section.

Radioplacentography results in delivery of about 5 millirads of radiation to the fetus. Thyroidal blocking is necessary with the use of agents labeled with I131 and Tc99m, although not with Cr51.12 However, the accuracy of radioplacentography in vertical localization of the placenta (98 per cent in this group of patients) far exceeded that of thermography in our hands, and is approached only by arteriographic methods delivering much larger amounts of ionizing radiation. Further, advances in photoscanning technique and the advent of ultrashort-lived radiopharmaceuticals now permit rapid placental scanning14 by which both placental position and morphology are delineated (Fig. 9) without an excessive radiation dose.

## SUMMARY AND CONCLUSIONS

Forty-four patients in whom the placental site was later verified were studied during the last half of gestation by two diagnostic techniques—radiopharmaceutic placentography and infrared thermal placentography. The accuracy of vertical placental localization by the thermal method was 50 per cent; incorrect localization occurred in

16 per cent and nonlocalization in 34 per cent. Ninety-eight per cent of the radio-pharmaceutic localizations were accurate. Of 5 cases of placenta previa, I was correctly identified thermographically.

On the basis of this investigation it is concluded that, despite its advantages, thermoplacentography is less accurate than radiopharmaceutic placental localization. In our hands, the high incidence of nonlocalization of the placenta and the false negative results in the presence of placenta previa limit the value of thermoplacentography as a diagnostic method.

Philip M. Johnson, M.D. Columbia-Presbyterian Medical Center 622 West 168th Street New York, New York 10032

## ACKNOWLEDGMENTS

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## THE RADIOISOTOPE BLOOD POOL SCAN\*

By FREDERICK J. BONTE, M.D., and THOMAS S. CURRY, III, M.D.†
DALLAS, TEXAS

FRIEDELL, who had developed one of the first comprehensive clinical radioisotope programs in this country, reasoned that if one of the ordinary constituents of blood were to be tagged with a radioactive tracer element it would be possible to visualize large collections, or pools, of blood, such as that within the chambers of the heart, by the new technique of radioisotope scintillation scanning. His associate, Rejali, implemented the idea, and in 1955 devised much of the technique of blood pool scanning as it is practiced today. Subsequently, 2 principal applications of this test have been described: (1) differential diagnosis between pericardial effusion and cardiomegaly\*,7,8,10 and (2) differential diagnosis of thoraco-abdominal midline masses.4

Blood pool scans may be performed with any modern, commercially available equipment. The tracer substance should be one which rapidly comes to equilibrium dilution in the blood stream and which maintains a reasonably constant level for the next 30 to 60 minutes.

I<sup>131</sup> human serum albumin was the tracer first employed, and this was later supplanted by I<sup>131</sup> iodipamide sodium.<sup>3</sup> This compound in turn now should give way to Tc<sup>99m</sup> labeled human serum albumin,<sup>6</sup> for early experience in our laboratory with this agent<sup>5</sup> suggests that it is unquestionably the tracer of choice. Radiation doses to specific organs and to the whole body are of the order of magnitude of, or less than, those which might be produced by equivalent roentgenographic studies.

We will illustrate some of the features of blood pool scanning from an experience of about 200 such scans performed in the Radioisotope Laboratory at Parkland Memorial Hospital since 1957.

## DETECTION OF PERICARDIAL EFFUSION

If a patient has apparent cardiomegaly by roentgen and physical signs but the decision between simple cardiac enlargement and pericardial effusion cannot be made without additional information, radioisotope blood pool scanning may be performed. In our laboratory the preferred tracer is Tc99m human serum albumin, which we have employed in doses of from 1.5 to 3.0 mc. Counting rates over heart and lung blood pools with this tracer are such that scanning speeds of up to 125 cm./ min. may be employed with commercial, 3 inch crystal scanning units, and more rapid speeds may be obtained with units which feature larger crystals.

The principle of the diagnosis of pericardial fluid by a radioisotope scan test is a simple one: the size of the scanned image of the normal heart blood pool should approximately equal that of the cardiac silhouette as visualized on an appropriate matching roentgenogram. This is usually an anteroposterior, mid-respiration roentgenogram made with the patient supine, and with the roentgen ray tube at a distance of at least 6 feet from the film. Cardiac size distortion may be further minimized by using a split-film technique of two exposures, in which the roentgen ray tube is positioned centrally first over the left half of the chest, with the right side of the film shielded, then over the right half of the chest with the left side of the film covered.

When enlargement of the cardiac silhou-

† Clinical Fellow in Radiology, the American Cancer Society, Inc.

<sup>\*</sup> From the Department of Radiology, The University of Texas Southwestern Medical School and Parkland Memorial Hospital, Dallas, Texas.

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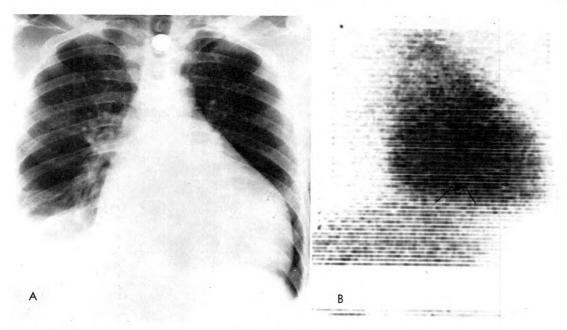


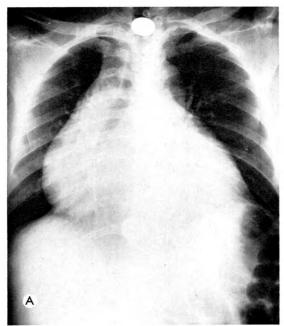
Fig. 1. (A) Six foot, anteroposterior, recumbent, midrespiration roentgenogram of the chest of a 43 year old male alcoholic with suspected pericardial effusion. Old pleural disease is seen at the right base. Pericardial effusion was not demonstrated by any tests and the patient was presumed to have cardiac enlargement due to nutritional heart disease. (B) Photoscan of cardiac blood pool made with tracer dose of 700 μc I<sup>131</sup> iodipamide sodium. Note reorientation marker for xyphoid process, and note also lesser blood pool in liver.

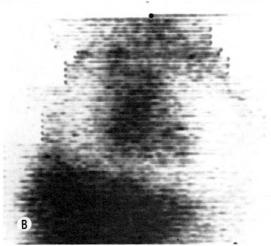
ette is due to enlargement of the heart, the silhouette should be matched by a large blood pool, as in Figure 1, A and B. When, however, silhouette enlargement is due to the presence of fluid in the pericardial sac, one would expect the true heart blood pool to be normal or perhaps even slightly reduced in size, as in Figure 2, A and B, the blood pool scan of a man who developed a voluminous pericardial effusion 6 weeks after a stab wound of the chest. Not only is there a notable discrepancy between the size of pool and silhouette but the body of pericardial fluid is actually seen in the photoscan as a zone of low radioactivity, or "belt," about the heart blood pool, delimited superiorly by tracer in hilar vessels, and laterally by radioactive blood within displaced and compacted pulmonary vasculature. The area between the heart and the liver is of especial importance, for normally heart and liver shadows are confluent (Fig. 1, A and B), while pericardial fluid is often visualized as a band of low radioactivity which separates the heart and liver isotope concentrations (cf. Fig. 1, A and B; and Fig. 2, A and B).

Figures 3 through 5, inclusive, show blood pool scans and their respective matching roentgenograms and illustrate the appearance of the inert belt phenomenon presented by effusions of decreasing size. The true volume of the effusion in the case shown in Figure 5, A and B, was probably not much greater than the 180 ml. removed by pericardiocentesis.

It is also interesting to note that the scans shown in Figures 3B and 4B were performed with I<sup>131</sup> iodipamide sodium and I<sup>131</sup> HSA, respectively. Each of these scans required about 40 minutes of scanning time. The scan shown in Figure 5B was made with Tc<sup>99m</sup> HSA and required but 14 minutes of scanning time.

As the volume of fluid in the pericardial sac becomes smaller, so does the accuracy of the scan test. Employing a heart-and-pericardium phantom system,<sup>3,5</sup> we were





able to demonstrate simulated 150 ml. effusions under relatively ideal laboratory circumstances. With either simulated or clinical effusions of less than this volume, the belt phenomenon is not apt to be seen on a photoscan and the diagnosis of effusion must then be based on comparison of the transverse diameter of the blood pool with the transverse diameter of the cardiac silhouette on the matching roentgenogram. If the pool/silhouette ratio falls below 0.8, effusion may be present, 10 but the method is far from infallible under these circumstances.

Fig. 2.(A) Six foot, anteroposterior, recumbent midrespiration chest roentgenogram of a 33 year old man with suspected pericardial effusion of traumatic origin. Note reorientation markers at suprasternal notch and xyphoid process. (B) Blood pool photoscan made with 750 μc I<sup>131</sup> iodipamide sodium shows small size of true heart blood pool. Note surrounding zone of lesser activity representing voluminous pericardial effusion. Note also separation of cardiac and hepatic blood pools by the fluid body (cf. Fig. 1, A and B). Confirmed volume of effusion was more than 1,500 ml. (Reproduced by permission from Southern Medical Journal.<sup>3</sup>)

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## MIDLINE MASSES

Among the early blood pool scans performed by Rejali *et al.*<sup>7</sup> was one made in the case of an elderly man who was known to have an aneurysm of the abdominal aorta. A large blood pool was easily demonstrated within it. We then decided to adapt blood pool scanning to the differential diagnosis of midline masses in the thorax and abdomen, much as one would use contrast roentgen angiography.

Once again, commercially available apparatus is satisfactory, although for the purposes of superimposing scan data upon matching roentgenograms we have commonly used a solenoid print rather than a photoscan, for the latter may obscure valuable roentgenographic detail. In the solenoid printing circuit of our scanner, data are processed by a background eliminator circuit. I<sup>131</sup> iodipamide sodium was formerly the tracer of choice for this application of blood pool scanning, but early experience indicates that here, too, Tc99m human serum albumin in tracer doses of from 1.5 to 3.0 mc shows sufficient promise to merit an extended trial. Reduction in patient radiation dose and an almost threefold reduction in scanning time are certainly important considerations.

Figure 6 demonstrates a large, abnormal blood pool which lies within a syphilitic

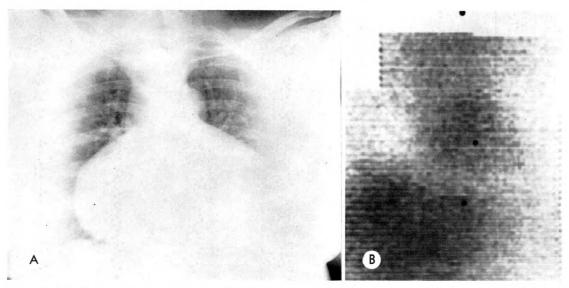


Fig. 3. (A) Six foot, anteroposterior, recumbent, midrespiration chest roentgenogram of a 47 year old woman thought to have pericardial effusion on the basis of contrast cinefluorography. (B) Blood pool photoscan made with 700 μc I<sup>131</sup> iodipamide sodium. Note separation of small heart blood pool from liver by belt of nonradioactive pericardial fluid. Cause and true volume of the effusion were never determined.

aneurysm of the thoracic aorta. Solenoid print scan data superimpose a 6 foot, anteroposterior, supine, mid-respiration chest roentgenogram. Note reorientation markers on scan and roentgenogram representing anatomic landmarks, such as the supra-

sternal notch and xyphoid process.

Vascular dilatations in the pulmonary arterial circuit are also identifiable as such by the presence of readily demonstrable blood pools as in Figure 7, A and B. When he was a child, this patient was found to

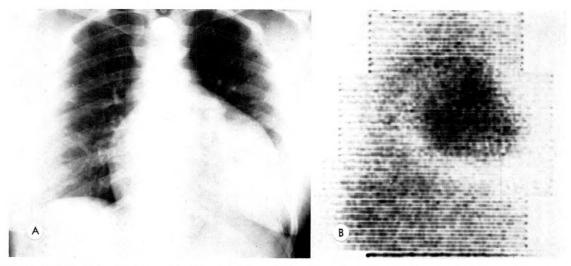


Fig. 4. (A) Six foot, anteroposterior, recumbent, midrespiration chest roentgenogram of a 42 year old woman with clinical evidence of myxedema: protein bound iodine = 2.0 μg./100 ml.; 24-hour I<sup>131</sup> uptake = 2.5 per cent. (B) Blood pool photoscan made with 750 μc I<sup>131</sup> HSA tracer. Note small size of real heart blood pool with zone of low radioactivity about it representing pericardial effusion of large but unknown volume. Note separation of cardiac blood pool from that of liver.

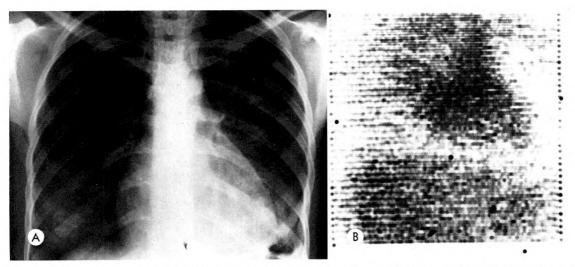


Fig. 5. (A) Six foot, posteroanterior, erect chest roentgenogram of a 22 year old woman who had received a gunshot wound of the left posterior chest wall 2 weeks before this study was made. Progressive enlargement of the cardiac silhouette had been observed. Note retained bullet fragment to the left of the centrum of the 11th thoracic vertebra. (B) Photoscan made with 1.6 mc Tc99m HSA tracer shows evidence of belt phenomenon along the left side of, and inferior to, a small blood pool. Pericardiocentesis yielded 180 ml. of blood-tinged fluid. This may have been the approximate volume of the effusion.

have tetralogy of Fallot and a shunt operation of the Potts' type had been performed. Over the years he had developed a large aneurysm of the pulmonary artery. Notice the large pool of blood localized within the area of the pulmonary artery, but note also the less satisfactory demonstration pro-

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duced by superimposing photoscan data rather than the solenoid print.

Figure 8 shows the roentgenogram and a superimposed scan of a man who had a large upper thoracic mass of unknown origin which did not contain a blood pool. It must thus represent either a solid tumor or an aneurysm largely filled with clot. It was identified by biopsy as a poorly differentiated squamous cell carcinoma.

Figure 9 shows a similar case, that of a woman who had a large left mid-mediastinal mass which might have represented metastasis from a known remote breast sarcoma, or possibly even a rapidly growing aneurysm, as was suspected by some of the physicians who had studied her case. No

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Fig. 6. Solenoid print scan made with 500 μc I<sup>131</sup> HSA is superimposed upon 6 foot, anteroposterior, recumbent, midrespiration chest roentgenogram. Note that scanned blood pool coincides with the shadow of known large syphilitic aneurysm of the aorta. (Reproduced by permission from J.A.M.A.<sup>4</sup>)

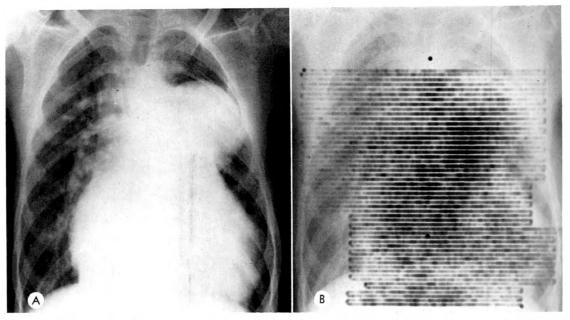


Fig. 7. (A) Six foot, anteroposterior roentgenogram made in deep inspiration and in semi-upright position. The patient was a 20 year old man with a history of remote Potts' operation performed for palliation of tetralogy of Fallot. A large aneurysm of the pulmonary artery had developed over a period of several years. (B) Photoscan data superimposed upon matching 6 foot, anteroposterior, recumbent, midrespiration roentgenogram. Scan performed with 680 μc I<sup>131</sup> iodipamide sodium shows large blood pool approximately corresponding to location of aneurysm.

blood pool can be seen within it on the scan, and it was presumed to be, and later anatomically shown to be, a metastatic tumor mass.

Detail of the distribution of blood within the volume studied may also be obtained. Figure 10 shows the distribution of blood within a great aneurysm of the aorta which involves its lower thoracic and upper abdominal portions. Note that the scanned blood pool does not approximate the palpable margin (dotted line) of the mass along its left inferolateral aspect. In this area surgeons later discovered a large mural clot.

The scan method is a fairly accurate one

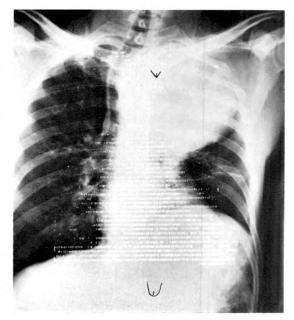


Fig. 8. Solenoid print scan data are superimposed upon matching 6 foot, anteroposterior, recumbent, midrespiration roentgenogram of a 51 year old man with rapidly growing left superior sulcus tumor mass, later shown to represent anaplastic carcinoma. Absence of blood pool is compatible with the diagnosis of solid tumor or aneurysm filled with clot. (Reproduced by permission from J.A.M.A.4)

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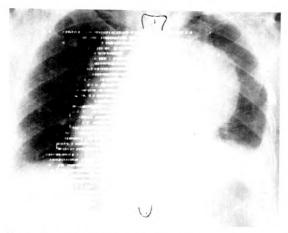


Fig. 9. Solenoid print blood pool scan data are superimposed upon usual matching roentgenogram of a 64 year old woman who had had a sarcoma of the left breast removed one year earlier. I<sup>131</sup> HSA scan shows no blood pool in rounded mass, thought to represent aneurysm clinically. Diagnosis of tumor metastasis was made on the basis of roentgenogram and scan, and was later confirmed at autopsy. (Reproduced by permission from J.A.M.A.4)

when employed to evaluate the presence or absence of a blood pool within a mass, the origin of which is unknown. In only 1 of 20 instances of midline thoracic tumefaction was a false diagnosis made. This was in the case of a very highly vascular mediastinal tumor in an adolescent boy, and the concentration of tracer was such that a diagnosis of aneurysm had to be made objectively.

## THE FUTURE

Radioisotope scanning is that branch of radiography in which the internally emitted photons of the radioactive tracer are employed to make a picture of the structure of interest. Each scan test must, therefore, compete with conventional external beam roentgenography when an equivalent roentgenographic procedure exists. In the case of the thyroid gland, the liver and the spleen, the scan reigns supreme, for there is not a satisfactory roentgenographic counterpart. In the case of renal, pulmonary and brain scans the radioisotope procedure supplies valuable supplementary information. Blood pool scans, however, must compete directly with angiographic contrast studies, some of which have been

fully developed only recently, and in this competition the radioisotope tests have languished.

Pericardial effusions which can be shown by blood pool scanning, i.e., those of at least 150 ml. volume, may be proven conveniently and rapidly by one of three roentgen procedures. The first and most commonly practiced is the roentgen-cinematographic examination of an intravenously injected 50 ml. bubble of carbon dioxide. The relationship between the superior margin of the bubble and the edge of the cardiac silhouette when the patient lies in the left lateral decubitus position is of decisive value in diagnosing or excluding pericardial effusion or thickening. Perhaps the most sensitive test is contrast angiography carried out with the patient in the right lateral decubitus position. It is likely that the smallest pericardial effusions can be detected by this method. A third tech-



Fig. 10. Solenoid print of I<sup>131</sup> HSA blood pool scan data is superimposed upon 6 foot, anteroposterior, recumbent, midrespiration roentgenogram of lower thorax and upper abdomen of a 51 year old man presumed to have a large syphilitic aortic aneurysm. Note that the thoracic component of the aneurysm elevates the heart well above the diaphragm. Dotted lines represent the palpable inferior margins of the process. Note blood pools in heart, liver and in all of the aneurysm except for a zone along its left inferolateral margin. At operation designed to correct the aneurysm, a large mural clot was demonstrated in the "cold" area. (Reproduced by permission from J.A.M.A.4)

nique involves the fluoroscopic examination of the subepicardial fat pad, a test which may not be applicable in each individual case. At any rate, one or all of these procedures have almost completely replaced blood pool scans in the detection of pericardial effusions, at least for the time being.

Further, impressive as the blood pool scan is in the differential diagnosis of midline masses, it must compete as a test with intravenous and selective intra-arterial contrast angiography and in most institutions, including our own, these roentgenographic procedures have supplanted radioactivity scan studies.

This state of affairs may change again, however. Recent experience in our laboratory with Tcoom, one of the family of low energy, short half life emitters, has shown us that when this element is used as Tc99m labeled human serum albumin it is effective in greatly reducing the time required to accumulate scan data, even with existing equipment, while simultaneously improving counting statistics and reducing patient radiation dose. Blood pool scanning times of the order of 12 to 15 minutes can be achieved with existing commercial apparatus with 3 inch crystal systems, and apparatus with larger crystals should yield even shorter scanning times. Stationary imaging devices<sup>1,2,9</sup> when fully developed, may require exposure times within the same general range as conventional radiographic techniques.

## CONCLUSION

We feel that blood pool scanning with some tracer such as Tc99m human serum albumin is now the procedure of choice for the detection of pericardial effusions and that it merits serious reconsideration as an alternative to roentgen angiographic techniques in the differential diagnosis of midline masses. In this area, as in many others, an era of rapid growth in radioisotope scanning is at hand.

Frederick J. Bonte, M.D. 5323 Harry Hines Boulevard Dallas, Texas 75235

The authors wish to acknowledge with gratitude the fine assistance provided in these studies by many radiology residents, some of them Fellows of the American Cancer Society, and by several excellent technicians including Miss Marguerite Youngman and Mrs. Marianne Little. Appreciation is extended to Dr. Paul Numerof, of the Radiopharmaceutical Division of E. R. Squibb & Sons for his kindness in providing I181 iodipamide sodium for some of these studies, and to Mr. D. R. Shumate, of Nuclear Consultants Corporation, for supplying Tc99m human serum albumin.

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# THE VALUE OF RADIOACTIVE CHLORMERODRIN FOR THE POSTERIOR FOSSA BRAIN SCAN\*

By CHARLES E. BENDER, M.D., and CLYDE M. WILLIAMS, M.D., Ph.D. GAINESVILLE, FLORIDA

X/IDESPREAD use of the brain scan as a screening method for detecting intracranial organic lesions was first carried out with radioiodinated serum albumin (RISA). Using this agent, supratentorial lesions were detected with an accuracy of about 80 per cent, but infratentorial lesions were less accurately localized. As a result, when a majority of users changed to radioactive chlormerodrin between 1961 and 1963, many workers abandoned posterior fossa brain scans in the belief that the results would be similar to those with RISA. Recently, Rhoton et al.17 have presented data indicating that radioactive chlormerodrin is as accurate in localizing infratentorial lesions as it is in supratentorial

The purpose of the authors is to confirm and extend their observations by recording 10 cases of histologically proven posterior fossa lesions. Our results show that, with the exception of acoustic neurinomas, posterior fossa lesions can be localized by radioactive chlormerodrin with an accuracy equal to that in supratentorial lesions.

## CLINICAL MATERIAL AND METHOD

Ten patients with histologically proven posterior fossa lesions have been studied by brain scanning with radioactive chlormerodrin prior to surgery, two commercially available scanning instruments being used. The majority of the scans were performed with a Picker Magnascanner having a 3 inch thallium activated sodium iodide crystal and a 19 hole focusing collimator. Scan speed usually was 28 cm./min., sweep separation 0.4 cm., density 75, range differential 20 per cent. The pulse height analyzer was set to accept x-rays from 27 to 127 kev. for the Hg<sup>187</sup> 77 kev. photopeak or

from 230 to 330 to accept the 280 kev. gamma ray from Hg203. The Hg203 labelled chlormerodrin was obtained from the Squibb Company and the Hg197 labelled chlormerodrin from either the Isoserve Corporation or the Squibb Company. All scanning procedures were preceded by a renal blocking dose of I cc. mercuhydrin. Scanning began between 1 and 2 hours after injection of the radioisotope. The posterior view was used initially if clinical suspicion pointed to the posterior fossa. When the posterior view suggested a right or left sided lesion, a lateral scan was made of the affected side. When the posterior scan revealed a midline or near midline lesion, both lateral views were obtained. The brain scan was usually the first special procedure to be performed.

## RESULTS

Ten proven cases of posterior fossa lesions were obtained from our records. Of these, 3 acoustic neurinomas could not be visualized. Six of the 7 remaining tumors were correctly localized.

## REPORT OF CASES

Case I. A 9 year old Negro male with ataxia, nausea, vomiting and headache of 2 weeks' duration was found to have an enlarged head, papilledema, a wide based ataxic gait and right dysdiadochokinesia. There was roentgenographic evidence of separated sutures and the electroencephalogram showed left hemispheric dysrythmia. The brain scans were interpreted as showing a large midline posterior fossa lesion (Fig. I, A, B and C). A right retrograde brachial arteriogram demonstrated a large midline posterior fossa lesion with associated tonsillar herniation and hydrocephalus. At surgery, there was found a large tumor  $(6 \times 7 \text{ cm.})$  replacing the vermis and displacing both cerebellar hemi-

<sup>\*</sup> Presented at the Southeastern Section of Nuclear Medicine, Memrhis, Tennessee, October 22-24, 1965. From the Department of Radiology, University of Florida College of Medicine, Gainesville, Florida.

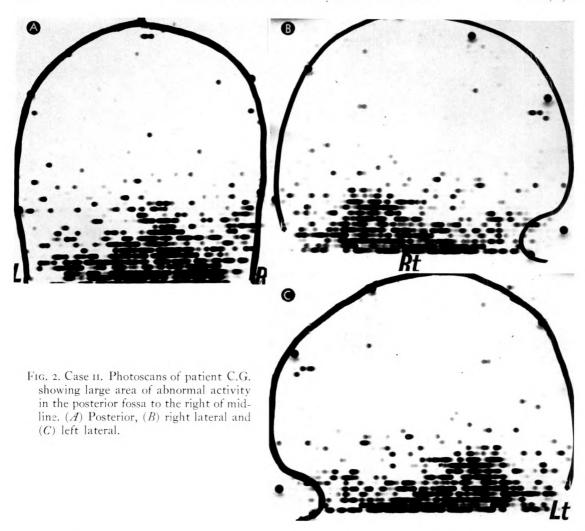


spheres laterally. The pathologic report was "low grade cerebellar astrocytoma."

CASE II. A 13 year old Negro male was admitted with a 4 week history of postoccipital headache, ataxia, right facial weakness, right hemiparesis, rigidity, dizziness, nausea and vomiting. On examination, there were found right ptosis and proptosis, diminished hearing in the right ear, lateral and rotatory nystagmus, bilateral papilledema and sixth and seventh nerve palsy. In addition, there were hyperesthesia of the right fifth nerve and ataxia. Skull roentgenograms revealed demineralization of the dorsum sellae and brain scans showed a posterior fossa lesion slightly to the right of midline (Fig. 2, A, B and C). A right retrograde brachial arteriogram demonstrated compression of the basilar artery against the clivus, suggesting a posterior fossa lesion. At suboccipital craniectomy, a mass was found protruding through the foramen magnum down to the level

of C-2. This mass compressed the medulla posteriorly and to the left and extended distally as far as the trigeminal nerve anterior-medially and into the pons. The seventh, eighth, ninth, tenth and eleventh cranial nerves were inextricably infiltrated with tumor, but after some 80 per cent of the neoplasm had been removed it appeared that the mass had originated in the pons. Pathologically, the tumor was reported as a Grade I astrocytoma.

Case III. A 7 year old Negro female with headache, right hemiparesis, progressive weakness, slowed speech, poor memory and nocturnal headache on neurologic examination was found to have paresis of the right fifth and sixth nerves, bilateral papilledema, right sided hemiparesis and hyperreflexia and an unsteady gait. Skull sutures were separated and brain scans showed a left posterior fossa lesion (Fig. 3, A and B). In a right retrograde brachial arteriogram, there was evidence of a large mass



originating in the left temporal region. At operation, there was found a large (9×8 cm.) poorly differentiated meningeal sarcoma originating from the tentorium. It extended both into the middle and posterior fossae and could only be partially removed.

Case IV. A 4 year old Negro female, referred for evaluation of progressive weakness and lethargy on neurologic examination, was found to be weak, obtunded and unable to walk. Skull roentgenograms were normal but an electroencephalogram showed a slow dysrhythmia with left central (prefrontal?) predominance. Brain scans showed an abnormal area (Fig. 4, A, B and C) of activity in the cerebellar fossa and in ventriculograms there were findings of a left cerebellar mass. A retrograde brachial arteriogram suggested a left cerebellar lesion.

At suboccipital craniectomy, a large malignant ependymoma (ependymoblastoma) was found and partially removed. The tumor occupied the lower half of the fourth ventricle and extended into the brain stem without a plane of demarcation. It bulged over the medulla at the foramen magnum and displaced the left cerebellar hemisphere and vermis towards the right.

Case v. A 69 year old white female was referred because of muscle weakness, dragging of the right leg, numbness of the right arm, and unsteadiness, all of 5 months' duration. Examination revealed right sided weakness and decreased sensation in the right upper extremity. A Babinski sign was present on the right. The Romberg test was negative. Spinal fluid pressure was 210 mm. and the protein was 91 mg. per cent. Skull roentgenograms, electroenceph-

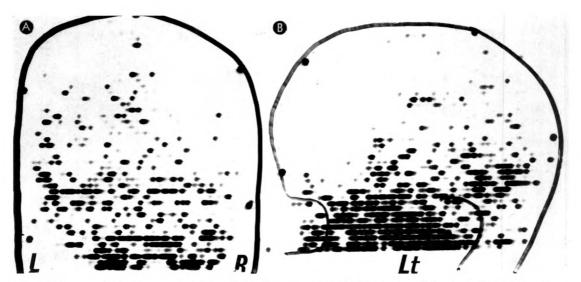
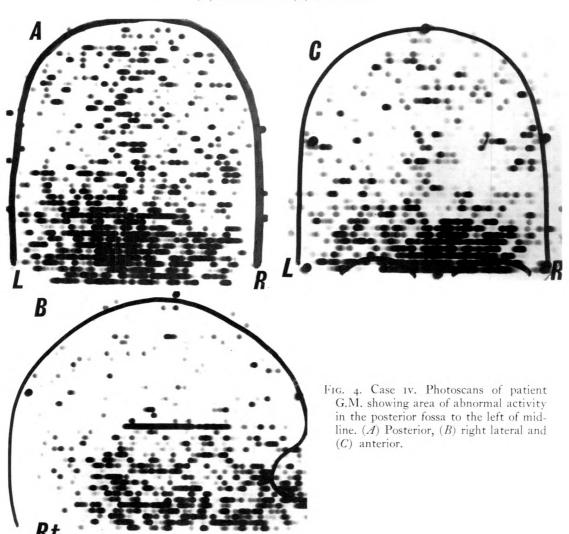
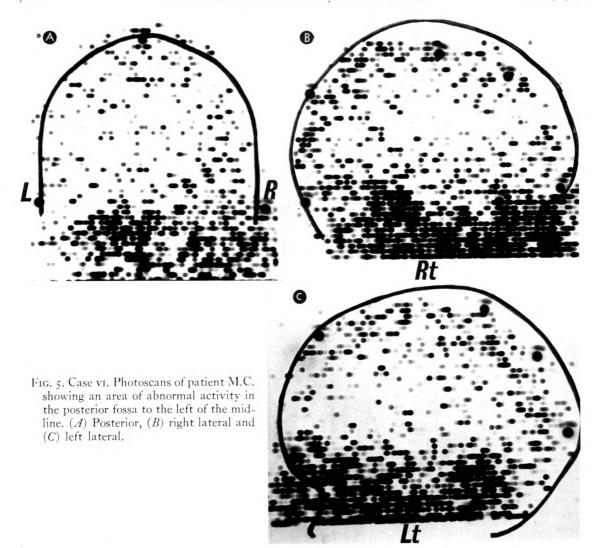


Fig. 3. Case III. Photoscans of patient C.W. showing area of abnormal activity in left posterior fossa. (A) Posterior and (B) left lateral.





alogram, and left carotid angiogram were normal. Brain scans were negative.

At suboccipital craniotomy, there was subtotal excision of a meningioma and laminectomy of C-I and C-2. A second stage operation was performed subsequently but complete removal of the tumor was impossible. In retrospect, it is possible that the failure to detect the tumor was due to a technical failure in failing to scan caudally enough in either lateral view. No abnormality was seen on the posterior view and we regard the case as a failure.

Case VI. This 60 year old white female had a 5 month history of weakness of the right lower extremity together with difficulty in bladder control. There had been several falls with inability to get up again. On examination, the

tongue deviated slightly to the right side and the gait was wide-based. The Romberg test was positive to the left.

The dorsum sellae was demineralized. Brain scans were positive in the left posterior fossa (Fig. 5, A, B and C). An electroencephalogram suggested a focal lesion in the right temporal area. A right retrograde brachial arteriogram was compatible with a lesion in the cerebellum, and demonstrated also hydrocephalus. Ventriculograms showed dilatation of the lateral and 3rd ventricle, kinking of the aqueduct of Sylvius and anterior displacement of a normal sized 4th ventricle. At operation, a left cerebellar meningeal fibroblastoma was found.

CASE VII. A 51 year old white female physician reported recurrent headaches for 6 years,

but without vertigo or other significant symptoms. Examination revealed decreased auditory acuity on the left but no motor or sensory deficit. Spinal fluid examination was negative, and an electroencephalogram and skull roentgenograms were normal. Brain scans were considered positive (Fig. 6, A and B) and ventriculograms showed a mass near the left petrous tip displacing the mid-brain. At surgery, a tentorial meningioma was found extending into both the middle and posterior cranial fossae. The patient expired several days following surgery.

## DISCUSSION

The supposition that brain scanning is of limited usefulness in the diagnosis of posterior fossa lesions originated from two widely quoted papers. Dunbar and Ray6 using RISA were able to localize only I posterior fossa neoplasm out of 5 proven lesions and in that case the increase in counting rate was borderline. McAfee and Taxdal9 demonstrated only 2 out of 6 posterior fossa tumors. Among the reasons which were given for these failures were: (1) the fact that masses in the posterior fossa are small compared with supratentorial lesions at the time when they first produce signs and symptoms, (2) the heavy mass of overlying occipital musculature, (3) the inconstancy in size of the dural sinuses, and (4) difficulty in positioning the patient for posterior scans. As a result of these and other reports, Murray,14 although using radioactive chlormerodrin, did not attempt brain scans in suspected posterior fossa lesions.

Since 1962, when we began to employ radioactive chlormerodrin, we have had an opportunity to scan 10 patients with histologically proven posterior fossa neoplasms. Three of these were acoustic neurinomas, all of which were missed. Six of the remaining 7 lesions were correctly localized. Because of our failure to detect acoustic neurinomas, we reviewed the recent literature, and divided the posterior fossa tumors into 2 groups: (1) acoustic neurinomas, and (2) other posterior fossa tumors. The results are shown in Table 1.

These reports indicate that excluding

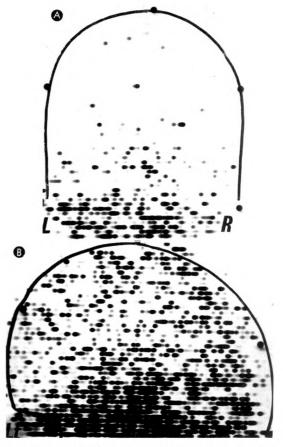


Fig. 6. Case VII. Photoscans of patient A.G. showing an area of abnormal activity above the temporal muscle area on the left lateral scan. The central position of the tumor prevents it from being well seen on the posterior scan. (A) Posterior and (B) left lateral.

acoustic neurinomas, the accuracy of localization of posterior fossa tumors is almost exactly that of supratentorial lesions when radioactive chlormerodrin (Table II) is employed for the scan.

McAfee and Fueger<sup>10</sup> have reported failure to localize 6 pontine gliomas using RISA or Hg<sup>203</sup> labelled chlormerodrin and have stated that no positive scan had been reported in pontine tumors. However, Bucy and Ciric<sup>2</sup> have reported a positive scan in a brain stem glioma. Goodrich *et al.*<sup>8</sup> have reported 2 positive scans in brain stem gliomas (although no histologic proof was obtained) in addition to our case of a pontine astrocytoma. All the latter positive

 $T_{ABLE\ I}$  proven cases of posterior fossa tumors scanned with radioactive chlormerodrin  $(Hg^{202}\ or\ Hg^{197})$ 

A dl	Acoustic Neurinoma			Other Posterior Fossa Lesions	
Authors	Total No. of Cases	Correctly Localized	Not Localized	Correctly Localized	Not Localized
Brinkman, Wegst and Kahn <sup>1</sup>	I			1	0
Bucy and Ciric <sup>a</sup>	15	I	3	7	4
Bull and Marryat <sup>3</sup>	2		J	2	ò
Goodrich, Tutor and Webster <sup>8</sup>	2			2	0
McClintock and Dalrymple <sup>11</sup>	4	I	0	2	I
McGinnis, Eyler, DuŚault	3	2	I		
Overton, Snodgrass and Haynie <sup>15</sup>	3	2	1	r	0
Rhoton, Carlsson and Ter-Pogossian <sup>16</sup>	12	0	1	10	ī
Sneider and Dooley <sup>21</sup>	I	I	0	I	0
Present Report	10	0	3	6	I
Total	53	7 (44%)	) 9	32 (82%)	) 7

scans were obtained with radioactive chlor-merodrin.

Our results are in agreement with those of Rhoton et al.<sup>17</sup> who attributed their success to the rapid renal excretion of chlor-merodrin, which decreases the radioactivity in the blood pool (dural sinuses) and reduces the obscuring radioactivity in the blood within the occipital musculature.

Failure to localize acoustic neurinomas is probably due to 2 factors: (I) the small size of most acoustic neurinomas when they first produce signs and symptoms, and (2) the fact that they are located at the border or behind the radioactivity produced by blood in the temporal musculature.

At a time when many workers are changing from Hg<sup>197</sup> labelled chlormerodrin to

 $Table \ II$  proven cases of brain tumors scanned with radioactive chlormerodrin (Hg\$^{107}) or Hg\$^{197})

Authors	Total No. of Cases	Correctly Localized	Per Cent
Brinkman, Wegst and Kahn <sup>1</sup>		60	65
Croll, Brady and Hand	6	5	83
Dugger and Pepper <sup>5</sup>	27	25	93
Feindel, Yamamoto, McRae and Zanelli7	69	56	88
Goodrich, Tutor and Webster <sup>8</sup>	24	22	92
McClintock and Dalrymple <sup>11</sup>	ુ૦	21	83
Mealey, Dehner and Reese <sup>13</sup>	23	18	78
Murray <sup>14</sup>	25*	22	88
Overton, Snodgrass and Haynie <sup>18</sup>	100	77	77
Rhoton, Carlsson and Ter-Pogossian <sup>16</sup>	20	17	85
Selverstone, Sweet and Robinson <sup>19</sup>	29	24	82
Sklaroff, Polakoff, Lin and Charkes <sup>20</sup>	20	17	85
Sneider and Dooley <sup>21</sup>	8	7	88
Total	473	371	78

<sup>\*</sup> Number of tumors not specified.

technetium 99m pertechnetate to take advantage of the tenfold increase in counting rate obtainable with the latter isotope, it would be well not to take for granted that all of the experience gained with radioactive chlormerodrin in brain scanning can be applied without modification to scanning with the newer isotope.

## SUMMARY

- 1. Ten surgically proven cases of posterior fossa neoplasms were examined by radioactive chlormerodrin brain scanning.
- 2. Three acoustic neurinomas were missed.
- 3. Six of 7 posterior fossa lesions were correctly localized.
- 4. A survey of the recent literature indicated that the accuracy of localization of acoustic neurinomas with radioactive chlormerodrin is about 40 per cent and all other posterior fossa tumors about 80 per cent, and that the latter figure is very nearly the same as the accuracy with which supratentorial tumors can be localized.

Charles E. Bender, M.D. Department of Radiology University of Florida Gainesville College of Medicine Gainesville, Florida

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## Tc<sup>99m</sup> IN THE VISUALIZATION OF NEOPLASMS OUTSIDE THE BRAIN\*

By J. E. WHITLEY, M.D., R. L. WITCOFSKI, M.S., T. T. BOLLIGER, M.D., and C. D. MAYNARD, M.D.
WINSTON-SALEM, NORTH CAROLINA

Tc<sup>99m</sup> pertechnetate has been utilized widely as an agent for the demonstration of benign and malignant lesions of the brain.<sup>2,4,7</sup> In the course of routine brain scanning, metastatic lesions of the calvarium were noted to concentrate pertechnetate (Fig. 1). This observation led the authors to undertake photoscanning of a series of cases with known extracranial tumors with Tc<sup>99m</sup>. The following report concerns the results obtained with these patients.

## MATERIALS AND METHODS

Twenty-six patients with known lesions were studied with photoscanning immediately after the intravenous injection of 3 to 5 mc of Tc<sup>99m</sup> pertechnetate. Picker Magnascanners with 3×2 inch crystals and 31 hole collimators were used in this study. With the spectrometer set at 130–160 kev., count rates were high enough to employ scanning speeds of 120–150 cm./min. Scans were begun within 5 minutes. In 4 cases, tissue samples (tumor and normal) were obtained at surgery 2 hours to 23 hours after injection for evaluation of isotopic distribution. These samples were counted in a well counter.

## RESULTS

The type of lesions scanned and the results of each are shown in Table 1. Seventeen out of 26 of the attempted scans were positive, that is, they showed greater radioisotope concentrations than did the surrounding normal tissue. Well demonstrated lesions, including a primary lung tumor (Fig. 2, A and B), a primary bone tumor (Fig. 3, A, B and C), and meta-

static bone lesions (Fig. 1; and 4, A and B) are illustrated.

To date, the results of tissue radioassay studies have not revealed a consistently elevated tumor/normal tissue ratio at the time of surgery. In this limited study, the radioactivity of whole blood samples was greater than that of most other tissues when compared on the basis of activity per gram.

## DISCUSSION

The primary demonstration of tumors due to their relative increased concentra-

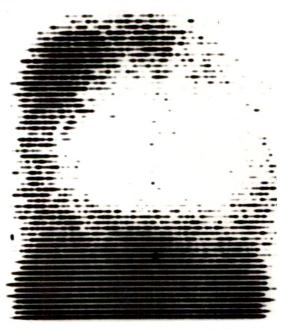


Fig. 1. Anteroposterior scan of the skull of a 45 year old white female with a biopsy proven metastatic adenocarcinoma. The isotopic distribution outlines the large osteolytic lesion in the right parietal bone which was identified on skull roentgenograms and was easily palpable (N.C.B.H. #41 08 33).

<sup>\*</sup> From the Department of Radiology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. This investigation was supported in part by USPHS Grant CRT 5069.

TABLE I

Case No.	Demonstrable Tc <sup>99m</sup> Concentration	Histologic Diagnosis	Primary or Metastatic	Site Scanned	Comments
1	Yes	Mucinous adenocarcinoma	Primary	Pancreas	Autopsy proven
3	Yes Yes	Mucinous adenocarcinoma Fibrosarcoma	Primary Primary	Lung Tibia	Sr <sup>85</sup> scan was also positive See Fig. 3, A, B and C
4	No	Ewing's sarcoma	Primary	Pubis	Radiation therapy just com- pleted
5	Yes	Anaplastic carcinoma	Primary	Lung	Biopsy came from bronchus See Fig. 2, A and B
6	Yes	Poorly differentiated ma- lignant tumor	Metastatic	Clavicle, humerus, pelvis	Primary site unknown. See Fig. 4, <i>A</i> and <i>B</i>
7	Yes	Adenocarcinoma	Metastatic	Skull	Primary site unknown. See Fig. 1
8	No	Papillary adenoma	Primary	Rectum	Tumor was "hot" by well counts. Rectal radioac- tivity obscured tumor?
9	No	Plasma cell leukemia		Skull	Small osteolytic lesions ap- parent on roentgenogram
IO	No	Chordoma	Primary	Sarcum	
11	No	Poorly differentiated malignant tumor	?	Rectum, anu	S
12	No	Carcinoma of the cervix	Metastatic	Liver	Probable tumor metastasis visualized by less activity than in the surrounding liver. Au <sup>198</sup> scan confirma- tion
13	Yes	Malignant lymphoma		Chest	Mediastinal
14	Yes	Poorly differentiated malignant tumor	?	Neck	
15	Yes	Presumed bronchogenic carcinoma	Metastatic	Tibia	Roentgenographic diagnosis
16	No	Poorly differentiated malignant tumor	}	Lung	
17	Yes	Presumed reticulum cell sarcoma	?	Thigh	Biopsy of neck lesion
18	Yes	Presumed hypernephroma	Primary	Kidney	Angiographic diagnosis
19.	No	Mucinous adenocarcinoma	Primary	Lung	
20	No	Alveolar cell carcinoma	Primary	Lung	Diffuse spread roentgeno- graphically
21	Yes	Poorly differentiated malignant tumor	ì	Lung	Biopsy of pleura
22	Yes	Adenocarcinoma		Lung	
23	Yes	Adenocarcinoma	<b>.</b> .	Lung	<b></b>
24	Yes	Carcinoma	Primary	Breast	Clinical diagnosis
25	Yes	Poorly differentiated malignant tumor	}	Lung	Scan was positive after 2 weeks of Co <sup>60</sup> therapy
26	Yes	Presumed adenocarcinoma	Primary	Cecum	Roentgenographic diagnosis

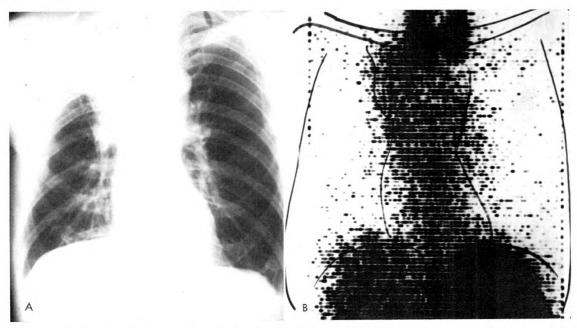


Fig. 2. Fifty-six year old white male with anaplastic carcinoma of the right lung involving the carina, right mainstem bronchus and occluding the right upper lobe bronchus (N.C.B.H. #41 23 37). (A) Postero-anterior roentgenogram showing a right hilar mass lesion with collapse of the right upper lobe. (B) Antero-posterior scan showing uptake of Tc<sup>99m</sup> in the region of the tumor and atelectatic right upper lobe. Note the normal landmarks of the blood pool of the heart and great vessels, the thyroid, the liver and stomach.

tion of radiopharmaceuticals is a well recognized and valuable technique in brain scanning. In most organs (liver, kidney, etc.), present day standard scanning techniques demonstrate lesions through diminished activity relative to surrounding normal tissue. The demonstration of neoplasms outside the brain through increased activity relative to the tumor bed and the surrounding tissues presents a different approach in their delineation. With this concept of scanning, others have reported the use of I131 serum albumin, Hg197 chlormerodrin, Ce131 and Sr85 in the study of extracranial tumors.1,3,5,6 Tc99m pertechnetate is reported as a scanning agent for tumors outside the brain worthy of further investigation.

The capabilities which make Tc<sup>99m</sup> an excellent brain scanning agent also apply equally to its extracranial utilization. Because of the 6 hour half life and the monoenergetic 140 kev. gamma emissions, relatively large doses may be administered while keeping patient radiation dose to

reasonable levels. The resulting high count rates permit rapid scanning. With most of the other compounds previously enumerated, scanning is usually performed hours to days after the administration of the compound. With the intravenous injection of pertechnetate, scanning can be begun immediately.

The initial tissue radioactivity results suggest the hypervascularity of many neoplasms, accounting for a large part of the obviously increased activity leading to their demarcation by scan.

Blood pools, such as in the heart, and other structures in which Tc<sup>99m</sup> collects, such as in thyroid, salivary glands, stomach liver, colon and bladder, may provide useful landmarks on the scans. However, these same structures may interfere with visualization of tumors in their immediate vicinities. Thus, the abdomen is a particularly difficult area. (The use of perchlorate is being investigated to suppress the uptake of the stomach, large bowel, etc.) It is also difficult to demonstrate small and/or deep-

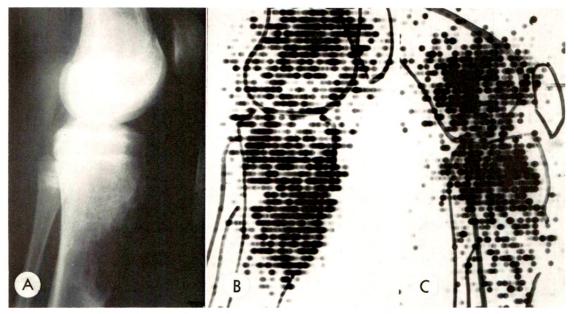


Fig. 3. Fifteen year old white female with a proven poorly differentiated fibrosarcoma (N.C.B.H. #41 29 53).

(A) Lateral roentgenogram showing the primary lesion in the proximal tibia. (B) Tc<sup>99m</sup> scan in the same projection demonstrating uptake by the tumor, the distal femur and proximal tibia. (C) Sr<sup>85</sup> scan in the same projection with a similar pattern of uptake about the knee, but relatively less uptake in the tumor.

ly situated pulmonary tumors even though their roentgenographic position is precisely known.

Scan interpretation is made on the basis of knowledge of the normal distribution

of Tc<sup>99m</sup> activity and by considering pertinent roentgenograms, other scans, and palpable findings.

It should be pointed out that the uptake of pertechnetate is not necessarily related

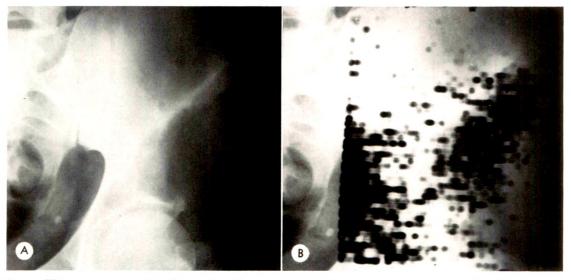


Fig. 4. Thirty-seven year old white male with a poorly differentiated malignancy, probably reticulum cell sarcoma, and multiple destructive lesions of bone (N.C.B.H. #03 15 22). (A) Anteroposterior roentgenogram of the left ilium demonstrating one of the large lytic lesions. (B) Roentgenogram and scan superimposed demonstrating the tumor by Tc99m. Note the normal bladder uptake medial to the ilium.

to malignancy. As in brain scanning, benign conditions may manifest themselves as positive scans. As an example, positive scans have been encountered in extracranial contusions and hematomas, and in cases of hyperostosis frontalis interna. The behavior of areas of infection and infarction is not yet evaluated.

The primary uptake of Tc99m pertechnetate by lesions of the central nervous system has revolutionized traditional neuroradiology. Tc99m scanning may potentially be useful in other areas where organs are not easily demonstrated by routine roentgenography or where routine techniques produce equivocal evidence of pathology. Hg197 chlormerodrin and Sr85 have already been suggested as useful agents in mapping therapy fields and in following the results of therapy, since they disclose more accurately than routine roentgenograms the extent of disease. Practical applications of extracranial Tc99m scanning remain to be investigated.

Despite the physical advantages of  $Tc^{99m}$  as a nearly ideal scanning agent with present day equipment, the compound or compounds of the future must be judged on their absolute selectivity of uptake in neoplastic tissue. An objective comparison of the previously mentioned agents including  $Tc^{99m}$  on the gross and cellular level is much needed.

#### SUMMARY AND CONCLUSIONS

Extracranial neoplasms have been visualized by scintiscanning as a result of Tc99m pertechnetate concentration within them. Seventeen of the 26 known neoplasms scanned were demonstrated, and

the compound seems worthy of further investigation. Pertechnetate as a scanning agent has the intrinsic advantages of immediate and rapid scanning and relatively low patient irradiation. However, it has the limitation of marked activity in normal blood pools and some normal organs, as well as in certain non-neoplastic lesions.

J. E. Whitley, M.D. Department of Radiology Bowman Gray School of Medicine Winston-Salem, North Carolina

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# EVALUATION OF LYMPH NODE FUNCTION FOLLOWING IRRADIATION OR SURGERY\*

By PRENTISS M. DETTMAN, M.D., E. RICHARD KING, M.D., and YALE H. ZIMBERG, M.D.
RICHMOND, VIRGINIA

PERHAPS the ability of lymph nodes to filter foreign or particulate matter plays a role in limiting the spread of certain cancers. Accordingly, study of the distribution of an injected particulate material following irradiation or surgical excision of the draining lymph nodes may be of potential clinical importance.

Colloidal gold (Au<sup>198</sup>) has the following characteristics that make it a suitable particulate material to study the filtering mechanism:

- 1. Its distribution can be measured and "scanned" with standard radioisotope equipment.
- 2. The short half-life (2.7 days) permits repeated study.
- 3. Sufficient activity can be contained in a small volume so that a possible volume effect is eliminated.
- 4. It is readily available and the commercial product well-standardized.
- 5. Gold is relatively inert and provokes little tissue response.

The fact that the Au<sup>198</sup> is radioactive is a disadvantage in a study of an external irradiation effect. A second disadvantage is the relatively small size of the colloidal gold particle compared to a cancer cell.

The dog was selected for this preliminary study because of previous experience with lymphangiographies in this animal.

#### TECHNIQUE

Five groups, as follows, were studied:

I—Controls

II—Three animals, surgical excision of right popliteal lymph node

III—Three animals, 2,000 r to right popliteal lymph node

IV—Four animals, 6,000 r to right popliteal lymph node

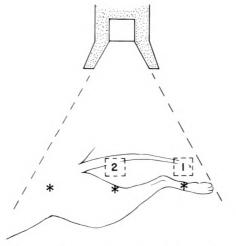
V—Two animals, 10,000 r to right popliteal lymph node

The controls consisted of the preliminary studies in each animal and the left hind limb of each animal. The popliteal lymph node excision was a simple excision with minimal trauma, not a radical dissection. The radiation was administered at 250 kv. peak, 2 mm. Cu half value layer, 50 cm. target skin distance, 400 r per day, Monday, Wednesday, and Friday, until the desired total air dose was obtained. A single anterior 4×4 cm. field encompassed the easily palpable popliteal lymph node (usually single).

Approximately 2-4 µc of undiluted colloidal gold in a volume of less than o.r cc. was injected subcutaneously cephalad to the posterior foot pad of the hind limb for each assay. Twenty-four hours later Au<sup>198</sup> distribution was analyzed by 2 techniques. The first is diagrammatically illustrated in Figure 1. A 2 inch NaI crystal detector was set at a distance of 70 cm. from the table top to minimize any geometric effect. The collimator encompassed an area, approximately 35 cm. in diameter at this distance. which included the injection site, popliteal lymph node, and the lower abdominal lymph nodes. No significant activity was noted to be localized outside this area in the study. The spectrometer straddled the 412 kev. gamma rays of Au198 with a 100 kev. window. Data collected, following

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<sup>\*</sup> Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.
From the Department of Radiology, Medical College of Virginia, and Department of Surgery, McGuire Veterans Administration Hospital, Richmond, Virginia.



#### DATA

BACKGROUND

NO SHIELDS

SITE OF INJECTION SHIELDED (1)

POPLITEAL SITE SHIELDED (2)

POP. AND INJECTION SITE SHIELDED (1-2)

Fig. 1. Diagram of one method of analysis of the colloidal gold distribution. Asterisks represent respectively from left to right the abdominal lymph nodes, the popliteal lymph nodes, and the site of injection.

determination of room background, consisted of total activity, activity with the site of injection shielded, activity with the popliteal lymph node site shielded, and activity with the site of injection and popliteal lymph node site shielded with lead blocks. The lead blocks were 7.5 cm. in diameter to easily encompass the area being shielded and 3 cm. thick (theoretic penetration of the 412 kev. gamma rays about 0.2 per cent). It should be emphasized that the determination of the percentage distribution of the colloidal gold in the various sites was exceedingly difficult because of geometry, scatter, shield penetration, and the relatively small number of counts which were present. A low dose was used for each assay to limit any inherent radiation effect (1 µc of Au<sup>198</sup> per gram of tissue could theoretically give a dose of about 65 rads at complete decay). Statistical significance was admittedly sacrificed.

Figure 2 shows the typical distribution with time for a normal animal from a previous investigation, utilizing a dose that far exceeded that used in this study so that the distribution could be followed for a long period. The Au<sup>198</sup> was divided between the site of injection, popliteal lymph node site, and what we have chosen to call "other." The "other" would include scatter, shield penetration, and most important, the ab-

dominal lymph nodes if activity were present there. It is in the latter area that we would expect localization of any material that penetrated or bypassed the popliteal lymph node. It should be noted that the distribution stabilized at about 12 hours post injection, and each distribution assay for this study was performed at 24 hours. A minimal interval of 2 weeks was allowed between assays in order to permit relatively complete decay from the previous study. The control limb was studied on a separate occasion from the treated limb to prevent any overlap of data.

The activity that leaves the site of injection is quite variable, depending on the total volume of material injected, the plane

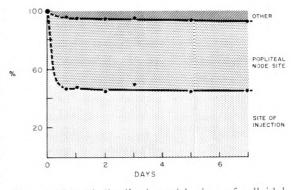


Fig. 2. Normal distribution with time of colloidal gold injected subcutaneously, cephalad to the posterior foot pad of the dog's hind limb.

of injection, the specific activity, site manipulation, etc.<sup>7</sup> Since only this activity was important in the present study (40–60 per cent of the dose), the results to be reported show only the distribution of material that has left the injection site. It is believed that this approach provides more meaningful data.

The second method of analyzing the distribution of Au<sup>198</sup> was by means of a "dot" scan. No "background erase" was used so the scan provided a more statistically significant distribution assay than the first method.

#### RESULTS

Figure 3 summarizes the data for the control group for the 6 month period of the study. In all cases more than 83 per cent of Au<sup>198</sup> that left the site of injection localized in the popliteal lymph node. In fact, only 2 values were less than 94 per cent, suggesting that the low values were due to poor statistics. A typical scan from a control animal is shown in Figure 4, confirming the distribution assay with no significant activity in any other areas but the popliteal lymph node (the site of injection is not included in the scan). No activity could be demonstrated definitely in the abdomi-

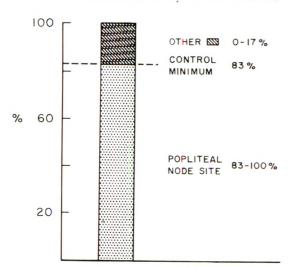


Fig. 3. Group I—Controls. Compiled data showing distribution of the colloidal gold that has left the site of injection with a normal popliteal lymph node.

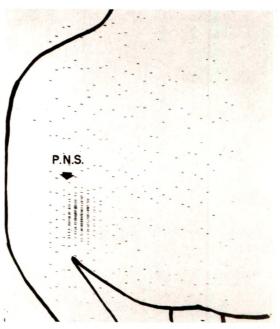


Fig. 4. Group I—Controls. Typical scan. P.N.S. indicates popliteal lymph node site. Site of injection is not included in the scan.

nal lymph nodes in any of this group by the scan.

Figure 5 shows the summated results of all the animals with popliteal lymph node

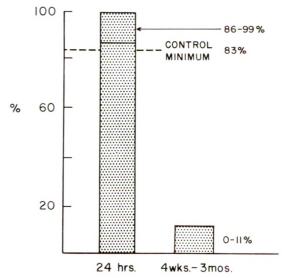


Fig. 5. Group II—Popliteal lymph node excised. Compiled data showing per cent of colloidal gold at popliteal lymph node site at 24 hours and from 4 weeks to 3 months following excision. (Considering only the Au<sup>198</sup> that has left the site of injection.)

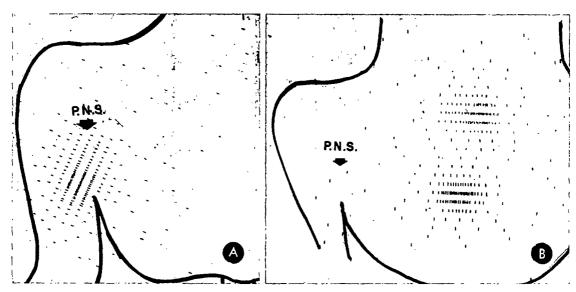


Fig. 6. Group II—Popliteal lymph node excised. (A) Typical scan at 24 hours. (B) Typical scan from 4 weeks to 3 months following excision. P.N.S. indicates popliteal lymph node site. Site of injection is not included in the scan.

excision. At 24 hours localization was still noted in the popliteal lymph node site, indicating that  $Au^{198}$  is probably collecting in the tissues from transected lymphatics. However, from 4 weeks to 3 months, an insignificantly small amount of  $Au^{198}$  was observed in the popliteal lymph node site and practically all of the  $Au^{198}$  that left the site of injection could be accounted for in the abdominal lymph nodes. Figure 6, A and B shows typical scans confirming the above data.

Figure 7 shows the summated distribution following 2,000 r to the popliteal lymph node area. There was no difference between these animals and the control animals and the scans were identical. The colloidal gold continued to localize in the popliteal lymph node.

The distribution of Au<sup>198</sup> that had left the site of injection at 6,000 r is shown individually for all animals for the entire period of study in Figure 8. It can be seen that in 2 animals (#313 and #316), beginning at approximately 2 months following irradiation, there was a significant decrease in the amount of material that had left the site of injection and localized in the popliteal lymph node site. In 1 other animal, the values after 1 month remained somewhat below those of the controls (#314). The behavior of the last animal was the same as that of the controls (#315). Figure 9,  $\mathcal{A}$  and  $\mathcal{B}$  shows typical scans of the animal with minimal evidence of failure of uptake in the popliteal lymph node (#314)

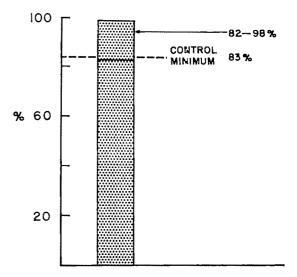


Fig. 7. Group III—2,∞∞ r to popliteal lymph node. Compiled data showing per cent colloidal gold at popliteal lymph node site following 2,∞∞ r. (Considering only the Au<sup>188</sup> that has left the site of injection.)

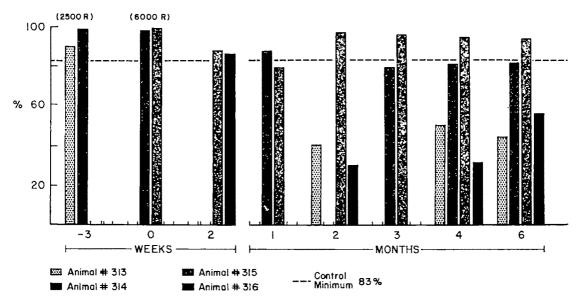


Fig. 8. Group Iv—6,∞00 r to popliteal lymph node. Data for each animal as indicated for entire period of study showing per cent colloidal gold at popliteal lymph node site. (Considering only the Au¹98 that has left the site of injection.)

and of the 2 animals with definite failure (#313 and #316). The scans of the remaining animal were identical to those of a typical control. The scans confirmed the distribution studies. Although some Au<sup>198</sup> reached the abdominal lymph nodes in 3

animals of this group, the popliteal lymph node continued to show evidence of colloidal gold uptake.

Only 2 animals were in the 10,000 r group since this is probably beyond the usual therapeutic levels. Figure 10 shows a sum-

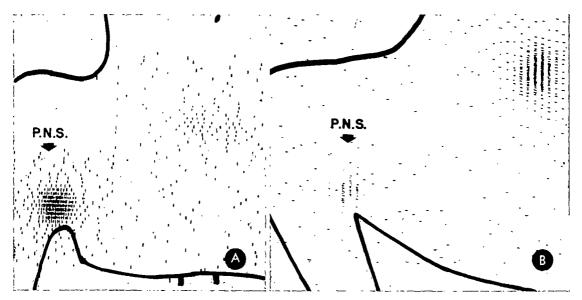


Fig. 9. Group IV—6,000 r to popliteal lymph node. (A) Typical scan of #314 confirming distribution of colloidal gold (Au<sup>198</sup>) in abdominal lymph nodes. (B) Typical scan of #313 and #316 showing definitely colloidal gold (Au<sup>195</sup>) in abdominal lymph nodes. P.N.S. indicates popliteal lymph node site. Site of injection not included on the scan.

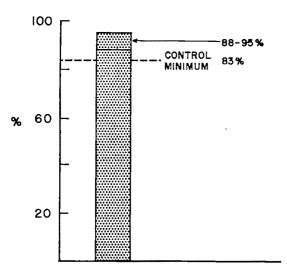


Fig. 10. Group v—10,000 r to popliteal lymph node. Compiled data showing per cent colloidal gold at popliteal lymph node site following 10,000 r. (Considering only the Au<sup>198</sup> that has left the site of injection.)

mary of Au<sup>198</sup> distribution for these animals. It is apparent that the distribution did not differ from that in the controls and this was confirmed by the scans. These animals developed marked fibrosis of the irradiated area.

Following completion of the above series, lymphangiograms were made and showed no gross abnormality in the irradiated group. The resected animals showed lymphatic continuity at the popliteal lymph node site with no evidence of lymph node regeneration (Fig. 11, A and B). Histologic comparison of the irradiated lymph nodes with normal lymph nodes showed no abnormality at 2,000 r, slight changes at 6,000 r, and definite changes at 10,000 r. Electron microscopy localized the colloidal gold in the so-called lysosomes or dense bodies in the macrophages of the lymph nodes.

At the conclusion of the study both animals in the 10,000 r group showed gross evidence of colloidal gold in the fibrotic tissue in which the lymph node was embedded. In one of the animals, a dose of colloidal gold was given 48 hours prior to dissection. Analysis showed almost 50 per

cent of the total activity at the lymph node site to be in the fibrotic tissue, but this could have included some lymph node capsule.

#### DISCUSSION

The distribution of the colloidal gold following simple excision of the popliteal lymph node is consistent with the recognized rapid restoration of lymphatic vessel continuity following transection. <sup>2,4,9</sup> Lymph node regeneration probably occurs only where the excision has been incomplete or in very young animals. <sup>4,5,9</sup>

The effect of irradiation of the lymph node site on the distribution of the colloidal gold is difficult to explain in view of the available histologic studies following irradiation. Apparently large doses are required to significantly alter lymphatics, probably in the range of the 10,000 r group in this study. 6,10 Fibrotic obliteration may result. The lymphocytes of lymph nodes show changes with small doses, but regeneration or repopulation is rapid.<sup>1,8</sup> Very large doses are required for marked permanent histologic distortion as shown in the 10,000 r group in this study. There is little evidence to support significant histologic changes with 2,000 or 6,000 r, which correlates with the histology from the animals so treated in this study.4,8

That no alteration in the distribution of the colloidal gold was observed following 2,000 r is therefore consistent with the histologic data. The fact that colloidal gold appeared in the abdominal lymph nodes in 3 of the 4 animals following 6,000 r to the popliteal lymph node site may be correlated with minor histologic alterations of the lymph node. This suggests that 6,000 r may be a threshold level. Bypass of the lymph node is another possibility but is less likely in view of the studies which have been made of the radiation effect on lymphatic vessels.

The fact that only 2 animals were used in the 10,000 r group makes the results less significant. However, the marked fibrosis

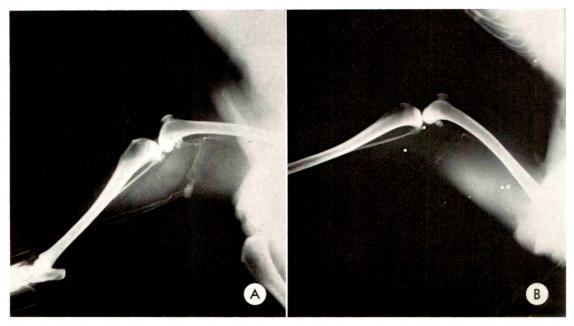


FIG. 11. (A) Lymphangiogram 6 months after 6,000 r showing normal popliteal lymph node. (B) Lymphangiogram 6 months after excision of popliteal lymph node showing continuity of lymphatics without evidence of lymph node regeneration.

that occurred in the irradiated site may be a satisfactory explanation for the lack of alteration in the colloidal gold distribution, especially in view of the gross evidence and differential assay at the conclusion of observation. In both of these animals, there was a beginning of breakdown at the irradiated site and we can speculate that bypassing lymphatics would develop.<sup>4</sup>

Studies in the human are made more difficult by the marked variability in distribution of a particular colloidal gold injection compared to the relatively simple system used in this study. Secondly, the presence of metastatic disease in the lymph nodes and/or inflammation appears to alter the picture significantly. The available evidence suggests, however, that normal lymph nodes do not lose all their ability to filter colloidal gold following the usual radiation therapy doses.

Further studies are indicated with larger particles and, ideally, with a system utilizing cancer cells. Certainly, the latter would be difficult to design. However, since the alteration of distribution following irradiation was so minor with even the minute colloidal gold particle, it is expected that a minimal effect would result.

#### SUMMARY

Following subcutaneous colloidal gold injection behind the posterior foot pad of the hind limb of the dog, practically all of the Au<sup>198</sup> that left the site of injection localized in the popliteal lymph node. If the popliteal lymph node was excised, initially the radioactive gold localized in the site, but by I month lymphatic continuity was re-established and the Au<sup>198</sup> localized in the abdominal lymph nodes. Following 2,000 r to the popliteal lymph node with orthovoltage roentgen rays at a usual therapeutic rate, colloidal gold continued to localize in the popliteal lymph node site as in the controls. With 6,000 r, 3 of 4 animals, beginning 2 months following irradiation, showed some Au<sup>198</sup> reaching the abdominal lymph nodes. With 10,000 r, the distribution of Au<sup>198</sup> was the same as that in the controls, probably because of the marked fibrosis that occurred. Irradiation did not entirely

eliminate the localization of colloidal gold in the popliteal lymph node site in any case, and it is postulated that with particles as large as cancer cells no alteration would be noted.

Prentiss M. Dettman, M.D. Medical College of Virginia Richmond, Virginia

We are indebted to Dr. M. N. Sheridan of the Department of Anatomy, Medical College of Virginia, for the electron microscopy.

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# THE EFFECT OF MALIGNANT NEOPLASMS ON ERYTHROCYTE *IN VITRO* UPTAKE OF I<sup>131</sup> TAGGED TRIIODOTHYRONINE\*

By MAJIC S. POTSAID, M.D.,† and GERALD M. KOLODNY, M.D.‡
BOSTON, MASSACHUSETTS

THAT hormones can play a vital role in the course a cancer takes is readily apparent from the responses obtained in some patients treated with this kind of agent. Neoplasms of certain secondary sex organs (e.g., breast or prostate) can be markedly affected by therapy with estro-

genic or androgenic drugs.

Thyroid hormone is also reported to affect the course of cancer, alone<sup>11</sup> and in combination with radiation therapy. 7 Sommers, 15 studying autopsied patients, found histologically completely normal thyroid glands in only 14 per cent of those with breast cancer compared with 65 per cent of those without cancer. Stocks<sup>17</sup> similarly found abnormal thyroid glands in 18.7 per cent of patients dying from cancer and only 3.9 per cent of patients dving from other causes. Areas of the world with high incidence of endemic goiter have been shown to be areas of increased incidence of malignant disease.16 Liechty, Hodges and Burket, 10 studying patients in a thyroid clinic, found a decreased incidence of cancer in thyrotoxic patients. The results of studies of I131 plasma and thyroid levels14 and 24 hour I131 uptake and conversion ratio12 in cancer patients were found to be consistent with decreased thyroid function.

The present study is a report on the *in vitro* uptake of I<sup>131</sup> labelled l-triiodothyronine by erythrocytes of 200 patients seen in a general hospital tumor clinic.

#### METHOD

Two hundred patients ranging in age from 14 to 85 years and 35 control sub-

jects (hospital personnel) ranging in age from 20 to 60 years were studied. The *in vitro* erythrocyte uptake of I<sup>131</sup> l-triiodothyronine (T-3 uptake) in these patients was determined according to the procedure of Hamolsky, Stein, Freedberg, and Golodetz.<sup>8,9</sup>

#### RESULTS

Table I lists the diagnosis, age, sex, and T-3 uptake of the patients studied. None of these had known thyroid diseases. There were 73 patients with breast cancer; 47 cases of lymphoma, leukemia, and polycythemia vera; 20 cases of carcinoma of the larynx, hypopharynx, mouth, and tongue; 8 cases of basal cell and squamous cell carcinoma of the face; 16 cases of adenocarcinoma of the gastrointestinal tract; 15 cases of cancer of the uterus, cervix, and vulva; and 21 other neoplasms. The 35 control subjects consisted of 17 males and 18 females. Their average T-3 uptake was 14.4 per cent with a standard deviation of  $\pm 2.4$ . Applying Student's T test, there was no significant difference between the male and female controls (T=0.1279 and P > 0.25).

Average T-3 uptakes of the largest groups of cancer patients are presented in Table II. Figure 1 is a graphic presentation of these data. Patients with cancer of the larynx, hypopharynx, and mouth and with basal and squamous cell cancers of the face had T-3 uptakes which were not significantly different from the normal controls (P>0.25). Gastrointestinal, breast,

(Text continued on page 724)

<sup>\*</sup> From the Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts.

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† Assistant Clinical Professor in Radiology, Harvard Medical School, and Associate Radiologist, Massachusetts General Hospital, Boston, Massachusetts.

<sup>‡</sup> Resident in Radiology, Massachusetts General Hospital, Boston, Massachusetts.

TABLE I
INDIVIDUAL T-3 UPTAKE VALUES

T-3 Jptake			Remarks	
3.4	59	F	Adenocarcinoma of breast	MANUFACTOR
0.6	40	F	Adenocarcinoma of breast	
10.9	70	F	Adenocarcinoma of breast	
13.2	60	F	Adenocarcinoma of breast	On estrogens
4.I	65	F	Adenocarcinoma of breast	On estrogens
9.3	55	F	Adenocarcinoma of breast	
3.4	75	F	Adenocarcinoma of breast	
1.2	67	F	Adenocarcinoma of breast	On estrogens
1.6	41	$\mathbf{F}$	Adenocarcinoma of breast	
5.0	75	$\mathbf{F}$	Adenocarcinoma of breast; Paget's disease	
8.7	75	$\mathbf{F}$	Adenocarcinoma of breast	
6.36	55	$\mathbf{F}$	Adenocarcinoma of breast	On estrogens
3.3	77	F	Adenocarcinoma of breast	
9.65	64	F	Adenocarcinoma of breast	
5.4	72	F	Adenocarcinoma of breast	On estrogens
8.8	44	F	Adenocarcinoma of breast	Castrated
0.4	77	F	Adenocarcinoma of breast	On estrogens
7.0	78	F	Adenocarcinoma of breast	
1.7	72	F	Adenocarcinoma of breast and leiomyomas	
6.4	67	$\mathbf{F}$	Adenocarcinoma of breast	
9.15	36	$\mathbf{F}$	Adenocarcinoma of breast	
9.4	45	$\mathbf{F}$	Adenocarcinoma of breast	
I.I	69	F	Adenocarcinoma of breast	
8.55	66	$\mathbf{F}$	Adenocarcinoma of breast	
2.9	73	F	Adenocarcinoma of breast	
3.8	66	$\mathbf{F}$	Adenocarcinoma of breast	
0.0	73	$\mathbf{F}$	Adenocarcinoma of breast	
3.5	47	F	Adenocarcinoma of breast	On cortisone
7.2	54	$\mathbf{F}$	Adenocarcinoma of breast	
2.4	68	F	Adenocarcinoma of breast	On estrogens
8.51	62	$\mathbf{F}$	Adenocarcinoma of breast	
6.9	84	${f F}$	Adenocarcinoma of breast	
8.9	46	F	Adenocarcinoma of breast	
8.2	44	F	Adenocarcinoma of breast	
2.9	72	$\mathbf{F}$	Adenocarcinoma of breast	
2.0	72	F	Adenocarcinoma of breast	On estrogens
6.9	87	F	Adenocarcinoma of breast	On estrogens
8.0	42	$\mathbf{F}$	Adenocarcinoma of breast	
8.2	67	$\mathbf{F}$	Adenocarcinoma of breast	
6.12	60	F	Adenocarcinoma of breast	
6.9	77	F	Adenocarcinoma of breast	
0.8	54	$\mathbf{F}$	Adenocarcinoma of breast	On androgens
0.9	52	F	Adenocarcinoma of breast	On steroids
2.I	48	F	Adenocarcinoma of breast	On steroids
5.0	70	$\mathbf{F}$	Adenocarcinoma of breast	On estrogens
6.7	59	$\mathbf{F}$	Adenocarcinoma of breast	On steroids
3.2	52	F	Adenocarcinoma of breast	On estrogens
2.8	78	Ē	Adenocarcinoma of breast	
8.3	72	F	Adenocarcinoma of breast	
1.6	50	F	Adenocarcinoma of breast	
8.6	60	$\mathbf{F}$	Adenocarcinoma of breast	

Table I—(Continued)

Optake	i-3 Age take (yr.)		Primary Tumor	Remarks
11.2	53	M	Adenocarcinoma of breast	
11.2	81	F	Adenocarcinoma of breast	
10.2	44	F	Adenocarcinoma of breast	
10.7	60	F	Adenocarcinoma of breast	
8.7	71	F	Adenocarcinoma of breast	On estrogens and steroid
6.6	64	F	Adenocarcinoma of breast	On estrogens
9.2	62	F	Adenocarcinoma of breast	J
8.8	50	F	Adenocarcinoma of breast	
9.5	83	$\mathbf{F}$	Adenocarcinoma of breast	On estrogens
11.4	42	$\mathbf{F}$	Adenocarcinoma of breast	<b>G</b>
9.8	54	$\mathbf{F}$	Adenocarcinoma of breast	On estrogens
8.8	73	$\mathbf{F}$	Adenocarcinoma of breast	On estrogens
13.7	56	$ar{\mathbf{F}}$	Adenocarcinoma of breast	
10.4	<del>4</del> 7	$ar{\mathbf{F}}$	Adenocarcinoma of breast	
15.3	43	$\overline{\mathbf{F}}$	Adenocarcinoma of breast	Castrated, on steroids
13.3	71	$\mathbf{\tilde{F}}$	Adenocarcinoma of breast	<b></b> ,
15.7	55	F	Adenocarcinoma of breast	
15.1	82	F	Adenocarcinoma of breast and colon	On androgens
9.0	59	F	Adenocarcinoma of breast and ovary	on unarogono
11.2	68	F	Adenocarcinoma of breasts (both)	
14.1	57	F	Adenocarcinoma of breasts (both)	On androgens
9.2	64	F	Adenocarcinoma of breast and stomach	on androgena
9.6	54	F	Adenocarcinoma of breast	
9.0	75	M	Lymphoma and basal cell carcinoma	
14.4	37	$\mathbf{F}$	Lymphoma	
10.1	35	$\mathbf{F}$	Lymphoma	
12.0	38	M	Lymphoma	
8.2	66	M	Lymphosarcoma	
7.95	73	M	Lymphoma	
7.25	59	M	Lymphoma	
9.8	70	F	Lymphoma	
10.3	40	$\mathbf{F}$	Lymphoma	
9.4	43	$\mathbf{F}$	Lymphoma	
9.5	68	F	Lymphoma	•
7.1	34	F	Lymphoma	
7.4	24	M	Lymphoma	
12.6	64	F	Lymphoma	
8.0	81	M	Lymphoma	
10.8	38	M	Lymphoma	
10.6	74	M	Lymphoma	
8.5	14	M	Lymphoma	
23.7	20	M	Lymphoma	
9.8	75	F	Lymphoma	
11.4	27	F	Lymphoma	
6.67	62	F	Lymphoma	
9.5	58	M	Lymphoma	
10.5	54	M	Lymphoma	
11.7	15	M	Lymphoma	
10.6	53	F	Lymphoma	
7.38	53 47	F	Lymphoma	
7.30				
10.9	16	$\mathbf{F}$	Lymphoma	

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Table I—(Continued)

T-3 Age Uptake (yr.) Sex				Remarks
7.65	29	F	Lymphosarcoma	
10.2	38	M	Lymphoma	On steroids
11.7	40	M	Lymphoma	
13.7	85	M	Lymphoma and basal cell carcinoma	
13.7	67	M	Lymphoma	
9.05	24	M	Plasma cell myeloma	
0.11	65	$\mathbf{F}$	Multiple myeloma	
9.0	80	M	Chronic lymphocytic leukemia	
8.65	69	M	Chronic lymphocytic leukemia	
9.0	62	F	Chronic myelogenous leukemia	
10.8	74	M	Lymphocytic leukemia	
3.3	83	M	Lymphocytic leukemia	
6.0	31	M	Monocytic leukemia	On steroids
10.55	62	M	Polycythemia vera	
6.5	78	M	Polycythemia vera	
10.0	68	M	Polycythemia vera	
13.0	66	M	Polycythemia vera	
18.4	80	M	Anaplastic carcinoma of larynx	
12.6	74	M	Carcinoma of larynx and hypopharynx	
13.8	61	M	Carcinoma of larynx	
13.4	42	M	Carcinoma of larynx	
2.7	56	M	Carcinoma of larynx	
7.6	70	M	Carcinoma of larynx	
4.5	56	M	Carcinoma of larynx	
5.0	45	M	Carcinoma of larynx	
4.0	78	M	Carcinoma of larynx	
4.2	51	M	Epiglottic carcinoma	
7.6	68	M	Squamous carcinoma of epiglottis	
12.6	67	M	Carcinoma of pyriform sinus	
2.9	55	M	Carcinoma of hypopharynx and squamous cell carcinoma of face	
12.5	65	M	Squamous cell carcinoma of tongue	
8.2	48	$\overline{\mathbf{F}}$	Squamous cell carcinoma of tongue	
5.I	55	M	Squamous cell carcinoma of tonsil and tongue	
9.9	65	M	Squamous cell carcinoma of tongue and esophagus	
9.9	28	F	Lymphoepithelioma of nasopharynx	
12.3	54	F	Basal cell carcinoma	,
0.11	82	M	Basal cell carcinoma	
6.7	80	M	Basal cell carcinoma	
9.8	<b>4</b> 6	M	Basal cell carcinoma	
2.2	61	M	Basal cell carcinoma	Hypertensive
4.4	66	M	Basal cell carcinoma	
8.3	79	M	Squamous cell carcinoma of face	
5.5	79	M	Basal and squamous cell carcinoma of face	
15.8	81	M	Squamous cell carcinoma of face	•
11.3	63	F	Adenocarcinoma of stomach	

Table I—(Continued)

9.7 17.4 10.5 8.7	57			
10.5		F	Adenocarcinoma of gallbladder	
_	73	F	Adenocarcinoma of colon	
8.7	73	M	Adenocarcinoma of colon	
	78	M	Adenocarcinoma of colon	
9.9	57	$\mathbf{F}$	Adenocarcinoma of colon	
10.0	60	M	Adenocarcinoma of colon	
11.7	55	F	Adenocarcinoma of colon and endometrium	
11.9	74	M	Adenocarcinoma of colon	
10.3	78	$\mathbf{F}$	Adenocarcinoma of colon	
9.8	7 <b>4</b>	F	Adenocarcinoma of colon	
9.2	59	F	Adenocarcinoma of colon	
13.2	59	F	Carcinoma of cervix	
11.6	52	$\mathbf{F}$	Carcinoma of cervix	
12.4	66	$\mathbf{F}$	Carcinoma of cervix	
12.7	38	$\mathbf{F}$	Carcinoma of cervix	
8.1	87	F	Carcinoma of cervix	
I4.I	57	$\mathbf{F}$	Carcinoma of cervix	
13.0	<b>4</b> 7	F	Carcinoma in situ of cervix	
9.35	73	F	Endometrial carcinoma	
7.6	70	F	Endometrial carcinoma	
9. I	66	F	Endometrial carcinoma	
29.3	77	F	Adenocarcinoma of uterus	
12.8	67	F	Carcinoma of uterus, and	On steroids
	٠,	-	adenocarcinoma of ovary	011 0101 0100
12.1	58	F	Squamous cell carcinoma of vulva	
10.1	59	F	Squamous cell carcinoma of vulva	
7.95		F	Pituitary adenoma	Military , - www.emys , www.ggmy, wwg.ggm
13.8	72	M	Kaposi sarcoma	
12.1	60	F	Polyp, vagina	
8.r	55	F	Benign tumor	
8.3	50	M	Metastatic adenocarcinoma	
12.1	75	M	Metastatic undifferentiated carcinoma	
7.7	55	F	Splenomegaly	
7.9	63	F	Hilus cell ovary tumor	
11.3	58	$\hat{\mathbf{M}}$	Granulosa theca cell tumor of testis	
11.0	60	M	Benign tumor	
11.9	60	F	Benign tumor	
19.8	74	M	Renal cell carcinoma	
9.5	59	M	Renal cell carcinoma with metastases	On steroids
16.4	64	M	Bladder sarcoma	0 0.0.0140
9.3	76	F	Squamous cell carcinoma, metastatic	On steroids
9.I	33	M	Malignant melanoma	J., 540.0140
15.8	73	F	Lipoma	
16.1	66	F	Fibrosarcoma	
9.8	52	F	Cavernous hemangioma	
12.3	6 <sub>4</sub>	M	Undifferentiated adenocarcinoma	
11.5	67	F	Parathyroid adenoma	
17.0	63	M	Adenocarcinoma of prostate	On steroids

Table II
T-3 UPTAKE VALUES BY TUMOR CATEGORIES

	No. of Patients	Avg. $T_{-3} \pm S.D.$
Normal	35	I4.4 ±2.4
Breast cancer (all)	73	10.6 ±3.08
On estrogens	14	9.64±3.1
On steroids	5	13.7 ±2.3
On no hormones	54	$10.55 \pm 2.97$
Lymphoma, Leukemia		
and Polycythemia	47	10.1 ±2.7
Gastrointestinal cancer	16	10.86±2.3
Carcinoma of larynx	10	14.5 ±2.0
Carcinoma of hypo- pharynx and mouth	10	14.1 ±3.15
Basal and squamous cell carcinoma of face	8	14.7 ±3.88

and hematologic cancer patients had T-3 uptakes significantly lower than the normal controls  $(P < 0.\infty1)$ .

Of the 73 patients with breast cancer, 14 were taking estrogenic hormones and 5 were taking steroid hormones. The average T-3 uptake of those patients taking estrogens was  $9.64\pm3.1$ . This value was not significantly different from the breast cancer patients not receiving hormones (T= 0.10 and P >0.25). The average T-3 uptake of those patients taking steroids was  $13.7\pm2.3$ , which was significantly different from the breast cancer patients receiving no hormone therapy (T=2.29 and P<0.03).

#### DISCUSSION

Although the present study is consistent with the results of Scott, Reilly and Searle<sup>14</sup> who found elevated levels of plasma I<sup>181</sup> and decreased thyroid uptake of I<sup>181</sup> in cancer patients and of Pastorelle, Turk, Collica, and Rubenfeld<sup>12</sup> who also found decreased thyroid I<sup>181</sup> uptake and conversion ratios in cancer patients, it is at variance with the study of Barrett, Berman, and Maier.<sup>1</sup> This last study reported T-3 uptakes on 3 patients with Hodgkin's disease. Two of these patients, in contrast to the present study, had T-3 uptakes higher than normal, whereas I of these patients, in agreement

with the present study, had a lower T-3 uptake than the normal. These same workers reported elevated T-3 uptakes in patients with polycythemia vera and in patients with "acute leukemia." Patients with polycythemia vera and leukemia in the present study, however, had decreased T-3 uptakes. There were no cases of acute granulocytic leukemia in the present study and the patients with "acute leukemia" in the study of Barrett, Berman, and Maier may have had granulocytic leukemia. Therefore, in regard to the leukemia patients, the 2 studies may not be comparable.

The increased T-3 uptake of breast cancer patients receiving steroid therapy over the breast cancer patients not on hormone therapy is consistent with the results of Friis and Reinicke<sup>5</sup> who found an increased T-3 uptake in 20 of 29 euthyroid patients treated with prednisone (30 mg./day for 1 to 9 weeks).

There have been many studies on the effects of estrogens on the thyroid gland and on thyroid function as measured by

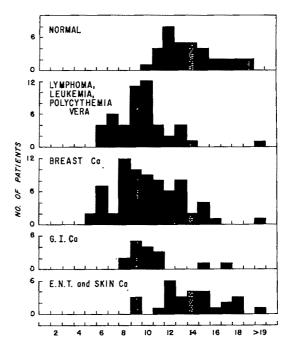


Fig. 1. Graphic comparison of T-3 uptake values for various tumor groups.

parameters other than erythrocyte T-3 uptake. These are reviewed by Farbman³ and again by Feldman.⁴ Some studies show increased thyroid function with the administration of estrogens while other studies show decreased or no change in thyroid function with the administration of estrogens. Still other workers have found that the effects of estrogens on the thyroid and thyroid function are a function of the dose of estrogens administered and the length of time the estrogens are administered.

Several workers<sup>6,8,9,13,18</sup> have found decreased T-3 uptakes in patients receiving estrogens. Although breast cancer patients receiving estrogen therapy in this study showed a significantly decreased uptake in comparison with the normal controls, they showed no significant decrease in comparison with the other breast cancer patients. Friis' patients had breast or prostate cancers and it is possible that the decreased T-3 uptakes in his series and the other reported series were the result of the patient's disease rather than the therapy.

One breast cancer patient in the present study received both estrogen and steroid therapy. The T-3 uptake in this patient was quite low, 8.7. This value, however, is consistent with the finding of Hamolsky et al.8 on 1 of their patients "who was receiving estrogens and had a normal uptake which decreased promptly on addition of cortisone therapy."

In the present study patients with squamous cell carcinomas did not show the decrease in T-3 uptake shown by the patients with adenocarcinomas and hematologic cancers. Why this should be so is open to conjecture. Circulating thyroid hormone is bound principally to one or more plasma proteins. According to current concepts,2,9 when I131 labelled l-triiodothyronine is added to a blood sample, any unbound protein sites are first saturated and then weaker binding sites on the erythrocytes bind the remaining T-3. Therefore, in hyperthyroidism, when there is saturation of protein binding sites by the endogenous thyroid hormone, the erythrocyte uptake of T-3 will be high. Conversely, in hypothyroidism, there will be many more protein sites available for the T-3 and the erythrocyte uptake will be low.

The current study suggests that in patients with adenocarcinomas and hematologic cancers there is either hypofunction of the thyroid gland or an increase in the plasma binding sites. Although it is possible that there is an increase in the total number of protein receptors or that these tumors produce a circulating compound which binds T-3, the studies of Pastorelle et al. 2 and Scott et al. 4 on I 181 uptake and of Liechty et al., 10 which showed a decreased incidence of cancer in thyrotoxic patients, suggest that the low erythrocyte T-3 uptake in patients with adenocarcinomas and hematologic cancers is the result of hypometabolism of the thyroid gland.

It is conceivable that the fragility of erythrocytes seen in some disease states such as leukemia may have in some way contributed to the low T-3 uptakes seen in many of the patients in this study. However, that explanation is not considered as a likely possibility.

#### SUMMARY

The *in vitro* uptake of I<sup>181</sup> labelled l-triiodothyronine (T-3) by erythrocytes of 200 tumor clinic patients and 35 control subjects was studied. Breast, gastrointestinal, and hematologic cancer patients had T-3 uptakes significantly lower than normal. Patients with cancer of the larynx, hypopharynx, and oral cavity, and basal and squamous cell cancers of the face had T-3 uptakes not significantly different from the normal controls.

Majic S. Potsaid, M.D. Department of Radiology Massachusetts General Hospital Boston, Massachusetts 02114

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### COMPUTER GENERATION OF NORMAL VALUES FOR THYROID I<sup>151</sup> UPTAKES\*

By ROBERT G. HOFFMANN, Ph.D.,† and CLYDE M. WILLIAMS, M.D., Ph.D. GAINESVILLE, FLORIDA

TWO general methods for establishing normal values of any laboratory test are: (1) to perform the test on apparently normal volunteers and (2) to accept patients with a suspected abnormality and, by long-term follow-up and other information, determine which were normal. The former procedure has obvious disadvantages where radioactive isotopes must be administered, but the second procedure is time consuming and extremely laborious. A computer program believed to be of wide applicability to clinical medicine has been written which promises to overcome the difficulties of the latter approach.2 The purpose of this paper is to describe the program and to illustrate its application to thyroid I<sup>131</sup> uptakes.

#### PROGRAM

Input to the program which is written in Fortran II for the IBM-709 is a series of consecutive tests on patients. No selection process is involved. The program (I) computes the normal range, (2) determines whether the testing procedures were stable during the time of testing, (3) does the necessary computations for establishing a measuring process quality control program based on patients' tests, and (4) transforms test measurement scale to one based on the normal range, i.e., "normal quotient units."

#### RESULTS AND DISCUSSION

Figure 1 shows a set of charts prepared from the computer printout. Input for this

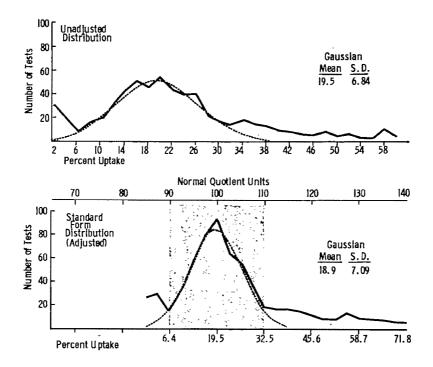
analysis consisted of 24 hour I181 uptake tests performed by conventional techniques on 650 consecutive patients referred to the Division of Nuclear Medicine of the Department of Radiology at the University of Florida College of Medicine. In the upper part of Figure 1, a frequency distribution of the tests is shown tabulated in class intervals of 2 per cent. A gaussian curve. shown as a dashed line, has been fitted to the frequency distribution in the neighborhood of the normal range. The curve fitting method used is essentially that of Hald. This gaussian curve is intended to be an estimate of the distribution which would be obtained if normal subjects had been tested for I131 uptake, and is referred to as the "central gaussian component" of the entire distribution.

Experience gained with working with approximately 40 different kinds of medical measurements indicates that measuring processes are not always stable. In the lower part of Figure 1 is an "average of normals" control chart, the purpose of which is to detect shifts in the measuring process. It was computed as follows: from the unadjusted distribution (Fig. 1, upper) the computer determines the normal range (gaussian mean ±2 s.d.). Beginning with the first test, it then examines each test to see whether its value is within the normal range. After it has located 10 "normal" tests, it averages them. For instance, the first average of normals on the left is approximately 18 per cent. The process continues until all tests have been examined, and where appropriate, included in an average. The dashed lines on the chart are 95 per cent confidence limits.

<sup>\*</sup> Detailed information about the program can be obtained by writing to one of us (R.G.H.) at the Computing Center of the University of Florida.

<sup>\*</sup> From the University of Florida Computing Center and from the Department of Radiology, University of Florida College of Medicine, Gainesville, Florida.

<sup>†</sup> University of Miami Branch, Coral Gables, Florida; Formerly Research Assistant Professor, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida.



Average of Normals Control Chart (10 tests per point, 95% confidence limits)

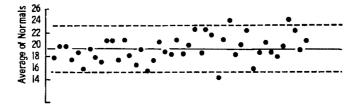


Fig. 1. (Upper) Frequency distribution of 24 hour I<sup>III</sup> uptake tests performed on 650 patients with suspected thyroid disease. The dashed curve is gaussian and is an estimate of normal patients' tests. (Middle) Frequency distribution of the same patients' tests adjusted for shifts in the testing procedure and tabulated in intervals of \(\frac{1}{2}\) standard deviation of normals. The dashed curve is gaussian and the shaded band is an estimate of the normal range. (Lower) "Average of normals" control chart. The dashed lines are 95 per cent confidence limits.

Each of the averages of normals is an estimate (approximately) of the midpoint of the normal range. Since normal patients as a group are stable, then if the testing procedure is stable, the averages of normals will not vary greatly, staying within the confidence limits approximately 95 per cent of the time. The chart seen in Figure 1 is typical of a stable testing procedure.

The chart in the middle of Figure I is a frequency distribution of the same patients' tests. The scale at the bottom of the figure is in per cent (thyroid uptake of I<sup>181</sup>)

but the class intervals are half-standard deviations of normals. Before the distribution was tabulated, correction also was made for shifts in the testing procedure as follows: after all of the averages of normals had been computed, the average of the averages was determined. When the averages of normals were computed, groups of tests which contain 10 normal tests were "blocked off." The adjusting process consists of comparing the average of the averages with the average of normals in each blocked off group. If the average of the

averages is the same as the average of normals, no adjustment takes place; otherwise, it adds to (or subtracts from) all tests in the blocked off group so that the average of normals is the same as the average of the averages.

After the tests have been adjusted, the computer transforms the measurement scale to a new scale called normal quotient units which is shown at the top of the middle chart of Figure 1. The normal quotient scale (n/q) is based on the standard deviation of normals and is thus independent of the original measurement scale. It was defined so that the midpoint of the normal range is 100 and the standard deviation of normals is 5 n/q units. With the normal range taken as ±2 standard deviations from its midpoint, then the normal range for any measurement expressed in these units is 90-110 n/q units. The shaded band on the chart identifies the normal range. The dashed curve in the middle chart again is a gaussian distribution. With a stable testing procedure, such as that illustrated by the data in Figure 1, there will be little difference between the unadjusted and the adjusted distributions. According to the results shown, the midpoint of the normal range is approximately 19 per cent and the normal range, about 6-32 per cent.

From the point of view of clinical experience, the normal range just defined needs further interpretation. Values immediately above the normal range are not always indicative of hyperthyroidism. There is a "doubtful range" where hyperthyroidism may or may not be present. Similarly, values immediately below the normal range are not always indicative of hypothyroidism, and there is also a "doubtful range" where hypothyroidism may or may not be present. These observations are a consequence of the fact that the thyrometabolic status of a patient is governed by the circulating "free" thyroxine level, a measure which affects and is affected by many parameters other than the thyroidal uptake of iodine. (An excellent example of an elevated I<sup>181</sup> thyroid value in a euthyroid patient occurs in pregnant patients where elevated liver production of thyroid-binding globulin results in an increased thyroidal synthesis of thyroxine and an increased circulating thyroxine level *but* a normal "free" thyroxine level and hence the eumetabolic state.)

The clinical records of the 650 patients were reviewed not less than 6 months after their original visit to the Nuclear Medicine Laboratory, and from all information available each patient was classified as hypothyroid, euthyroid, or hyperthyroid. The criterion for a confirmed diagnosis of hyperthyroidism or hypothyroidism was improvement or complete remission of clinical signs and symptoms of the disease after appropriate treatment. Frequency distributions by I<sup>131</sup> for each of these 3 patient groups are shown in Figure 2. A gaussian curve has again been fitted to the central component of the euthyroid distribution. Note how closely the gaussian mean and standard deviation correspond with those of the distribution shown in Figure 1.

The gaussian curve in Figure 2 does not include a substantial proportion of the euthyroid patients because of the marked skewness of the euthyroid distribution. The tail of the distribution, however, includes a number of the hyperthyroid patients. There is thus justification for defining a "doubtful range." It has been defined here as \frac{3}{4} the normal range above the upper limit of normal (15 normal quotient units). It is obvious from the considerations above and from study of the distributions in Figure 2 that no single range can be defined which will yield unequivocal diagnoses for all patients. Thyroid uptake of I<sup>181</sup> alone cannot determine for some patients whether a thyroid malfunction is present. Similar observations have been made in the case of 6 hour I<sup>131</sup> uptakes.4 With the criteria suggested, however, the uncertainty can be reasonably well defined.

It is not to be inferred that these results apply to all hospitals where I<sup>131</sup> thy-

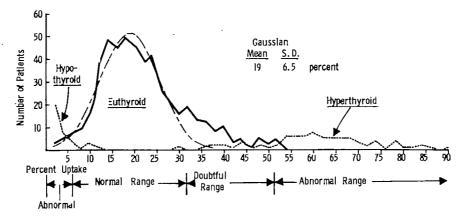


FIG. 2. Frequency distributions of 24 hour I<sup>M</sup> uptakes performed on 650 patients who were divided into hypothyroid, euthyroid and hyperthyroid categories by examination of their follow-up records. Separate distributions are shown for hypothyroid, euthyroid and hyperthyroid patients. The dashed curve fitted to the euthyroid distribution is gaussian.

roid function tests are performed. Experience with results of other tests performed at different hospitals indicates that laboratories may operate at different levels and with different degrees of accuracy and precision.

#### SUMMARY

A computer program written in Fortran for the IBM-709 has been described which performs the following operations on unselected consecutive tests: (1) computes the normal range, (2) determines whether the testing procedure was stable and (3) transforms the test measurement scale to one based on the normal range, *i.e.*, "normal quotient units."

The program was tested on 650 consecutive cases of patients with suspected thyroid disease, referred to the Department of Radiology of the University of Florida College of Medicine, on whom follow-up

information of at least 6 months was available. The validity of the computed normal range of 24 hour I<sup>131</sup> uptakes was established by examining the distribution of euthyroid patients after their status had been determined clinically.

Clyde M. Williams, M.D. Department of Radiology University of Florida College of Medicine Gainesville, Florida

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# DESIGN AND TESTING OF COLLIMATORS FOR EXTERNAL COUNTING OF Co<sup>57</sup> B<sub>1</sub>. IN THE HUMAN LIVER\*

By B. T. MOORE, M. A., with the technical assistance of JANE G. HEGEMAN ALBANY, NEW YORK

EXTERNAL scintillation counting of Co<sup>57</sup> B<sub>12</sub> from the human liver with collimated probes, when properly done, can be one of the most valuable nondestructive techniques currently known for obtaining information relative to organ uptake, duration and disappearance.

The counts obtained during external scintillation counting of the human liver may be a function of several variables. Some of these are: type of collimators, probe position, probe angle, organ size and depth and bordering, and underlying organs. Because of these factors, an investigator may have some doubts as to the origin of his detected counts and the validity of his data. It was our belief that properly designed and rigorously tested collimators could minimize and identify nearly all variables and give the investigator a greater degree of confidence in his data.

This study included: (a) design of collimators; (b) testing of collimators; and (c) quantitative analysis of radiation detected within the field of collimators.

#### GENERAL CONSIDERATIONS

The liver can be thought of as having 3 dimensions, that is occupying the X, Y, and Z planes. The geometry of a field encompassed by a collimator can be described as a frustum of a cone composed of circles of finite thickness with increasing diameters. The radius of each circle, as a function of distance, can be exactly defined. The isoresponse segment of tissue can be thought of as a parabola describing a volume of revolution. The environment of the liver can be described as an attenuating mass.

The geometry of a collimator, as compared to the isoresponse curve, has a

smaller significance due to the fact that for the same collimator it is a relatively fixed geometric figure. For the same collimator, the shape of the isoresponse curve depends upon additional factors, such as energy of the isotope, thickness of the collimator, or whether or not a point source or an extended source is involved.

A collimated probe can be compared to a light source in a round metal tube. The front end of the tube can be compared to the entrance aperture of a collimator. The light source situated within the tube can be compared to the detecting crystal within the collimator. If the light source is moved toward the aperture of the pipe and the light projected upon a wall, a definite sized light spot can be observed. When the light source is moved back from the aperture, the light spot can be observed to be relatively smaller. If the end of the pipe is now shaped into a flare or cone, the light spot on the wall will increase and decrease in size, respectively, with no movement of the light source within. Comparatively, the volume that a detector "sees" is a function of (a) diameter and length of the collimator; (b) the thickness of the collimator; and (c) the geometric shape of the collimator, i.e., whether it is flared, tapered or shaped otherwise.

#### MATERIAL AND METHODS

#### A. DESIGN OF COLLIMATORS

A Baird-Atomic Model 812B scintillation probe with a 1½ inch diameter by 1 inch thick NaI (Tl) crystal was used. Two collimators were designed and constructed by first determining the geometry required to see the liver at its depth, exclusive of other organs. The length or width of the liver or any segment thereof represents the diame-

<sup>\*</sup> From the Radioisotope Service, Veterans Administration Hospital, Albany, New York.

ter of a circle whose circumference is easily known. This circumference was made to situate within the boundary of the liver which would represent a liver segment. Two lines were projected out, one from each end of the circle's diameter, so that they described a geometry. Then we designed, fabricated and adapted the collimators to fit this calculated geometry. The required thickness of the lead for maximum attenuation was determined for the energy of this isotope for collimator thickness as a function of distance from the crystal. The designed collimaters were designated A and B (Fig. 1).

#### B. TESTING OF COLLIMATORS

Isoresponse curves were determined for collimators A and B with a 0.5 cc. source of Co<sup>57</sup> situated within a 11×12×17.5 inch plastic tank filled with water. The fall-off factor for an extended source was tested by placing a 2,000 cc. volumetric flask containing 1,700 cc. of water into the above

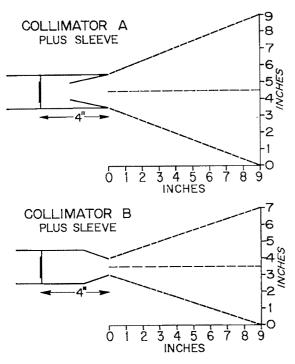


Fig. 1. Shape and geometry of collimators A and B.

The geometry is shown as a function of distance from the end of the collimators.

mentioned tank. Remcal,\* a standard plastic man was constructed to especially contain the following organs, some of which localize B<sub>12</sub> in man: thyroid, heart, lung, liver, kidney, spleen, stomach and intestine, pancreas, and brain. However, all organs were not used in this study due to their low B<sub>12</sub> localizing capacity.<sup>1</sup>

#### C. SITE PLACEMENT OF COLLIMATED PROBE

A placement site of the probe was determined which would eliminate most counts from organs other than the liver. Radioactive Co<sup>67</sup> B<sub>12</sub> was put in all organs except the liver. Two positions of counting were tried: No. 1 was over the xyphoid process; No. 2 was a position flush with the body surface at the midclavicular line midway between extremes of liver dullness.

#### D. TESTING FOR EFFECT OF CHANGES OF COLLIMATOR POSITION AND ANGLE

The No. 2 position on Remcal was used for the original count. The probe was then moved 2 cm. to the left, right, up and down. Counts were taken at each position and compared to the counts of the original counting position. A krollometer,† a special type of angle measuring device with no metallic parts to ensure noninterference with the photomultiplier tube performance, was used to measure the angle of the collimated probe at the No. 2 position. The probe angle was changed 5 degrees up, down, left and right. Counts were taken at each position and compared to the counts of the original counting angle. In each case, the counts obtained from sites other than the original site were compared to the counts obtained at the original site as a percentage difference in counts.

#### E. TESTING OF COUNTS FROM OTHER ORGANS

Remcal and its organs were filled with water. Co<sup>57</sup> was put into each organ at separate times, *i.e.*, when Co<sup>57</sup> was put into the kidney, no other organ contained Co<sup>57</sup>. By this method Co<sup>57</sup> was put separately into the spleen, heart, lung, kidneys, stom-

<sup>\*</sup>Constructed by Alderson Research Laboratories, Inc., Long Island City, N. Y. †Purchased from Federal Supply Service.

ach, and intestine The liver which contained no Co<sup>57</sup> was used as the counting site. The counts detected at the liver in each case were noted. The above method was also used to compare the designed collimators to the following: (a) standard collimators; (b) shielded probe with no collimator; (c) shielded probe with collimator and sleeve; and (d) designed collimator with no sleeve. The sleeve will be discussed further in the text.

#### F. TESTING COLLIMATOR EFFICIENCY

Co<sup>57</sup> was put into the liver, exclusive of all other organs, and counted at this site with collimators A and B. The count/min./ µc for each was observed.

#### G. TESTING BY SPECTRAL RESPONSE

Co<sup>57</sup> was put into the liver of Remcal. No other organ contained Co<sup>57</sup>. A spectrum was run on the liver and compared to the spectrum of a patient who had previously had Co<sup>57</sup> B<sub>12</sub>. Collimator A was used for this procedure.

#### H. ANALYSIS OF ISORESPONSE CURVE

The positive part of an isoresponse curve represents a near parabola. One should think of the positive or upper part as rotating around the X axis. In doing this, a volume of revolution would be described. The total isoresponse curve or any per cent curve could be analyzed as to the volume contained within it by the formula:

$$V=\pi\int_{X_1}^{X^2}y^2dX,$$

where V=volume, y=radius at the base of the curve. Using this method, the approximate volume of tissue contained within the 5 per cent curve of collimator A was calculated.

#### RESULTS

Collimator A consisted of a modification of a commercial collimator. We fabricated a 3 inch long  $\frac{1}{2}$  inch thick lead "sleeve" to a 2 inch diameter collimator. This sleeve is removable so that the collimator can be used for other purposes. The final design of collimator B was an "inverted cone" with

a I inch entrance aperture that expanded to approximately 2 inches at the crystal. The removable lead sleeve was also included in this collimator. The geometric field of the designed collimators is shown in Figure I. The radius and diameter of the frustum as a function of distance from the collimator end can be seen.

Figure 2 shows the isoresponse curve for collimator A. One can note that the curve falls off to 1 per cent at a radius of 12 cm. and that the radius of the 10 per cent curve is approximately 4 cm. The per cent of fall-off of counts as a function of distance for an extended source is shown in Figure 3, A and B. The formula  $I = I_0 e^{-0.100L}$  for collimator B describes the count fall-off as a function of organ depth, where I = detected radiation at a specific organ depth and  $I_0 =$  radiation at 0 cm.

When tried on patients, the better probe site placement for liver counting was found to be the position No. 2 due to less count variation. This position was flush with the surface midclavicular line midway between the extremes of liver dullness. Figure 4A shows the position relative to the human body. The angle shown is from the deter-

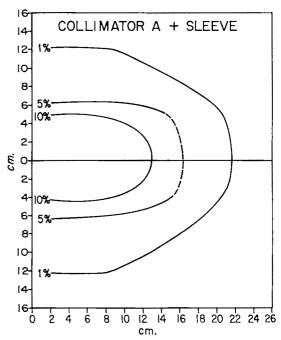
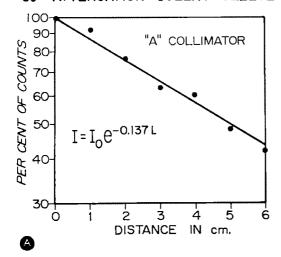


Fig. 2. Isoresponse curve for collimator A plus sleeve.

## Co<sup>57</sup>ATTENUATION-COLL. A + SLEEVE



## Co<sup>57</sup>ATTENUATION - COLL. B + SLEEVE

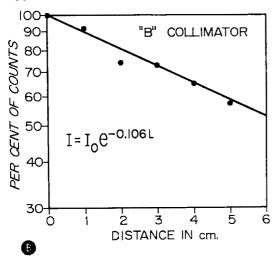


Fig. 3. (A) The per cent count fall-off for collimator A as a function of distance from an extended source. (B) The per cent count fall-off for collimator B as a function of distance from an extended source.

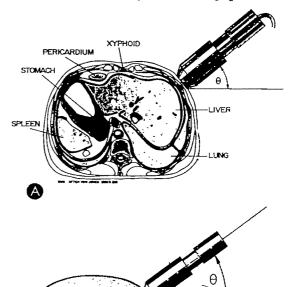
mination of one angular position. The determination of the angular positions is shown schematically in Figure 4B. It shows that one probe position is defined by two angles. Table 1 shows the results of per cent count drop-off due to 5° angular change of collimator and a 2 cm. site change of probe position. The range is from 0 to 6 per cent.

The results of testing of counts from

various organs with the probe at the liver site are shown in Table II in terms of count/min./ $\mu$ c. Co<sup>57</sup> was put into the organs one at a time and none was in the liver. Table III compares the count/min./ $\mu$ c to the designed collimator B in terms of ratios. Collimator B at the liver site, compared to standard collimators, reduced the counts originating from the kidney 8 and 19 fold. Other reductions can be noted. Comparing the count/min./ $\mu$ c of collimator A and B at the liver site of Remcal, collimator A was found to have an efficiency approximately 3 times that of collimator B.

The spectrum resulting from the Remcal liver that contained Co<sup>57</sup> exclusive of all other organs was compared to the spectrum resulting from a patient's liver who had previously had B<sub>12</sub> (Fig. 5). The close similarity is evident.

The volume analysis of the 5 per cent



B

Fig. 4. (A) Probe position relative to human body.

Angle  $\theta$  denotes the determined angular position on the X-axis for a fixed probe position. (B) Probe position described by angular determination on

X-axis and Y-axis for a fixed probe position.

X-AXIS

Table I

PER CENT DROP-OFF DUE TO CHANGE OF

PROBE ANGLE AND POSITION

5° Change	Up	Down	Right	Left
Collimator A	5%	1%	3%	6%
Collimator B	4%	0%	3%	4%
2 cm. Change	Up	Down	Right	Left
Collimator A Collimator B	5%	2%	4%	2%
	5%	1%	3%	2%

isoresponse curve is shown in Figure 6, from which it can be noted that its volume is 2,783 cc.

#### DISCUSSION

External scintillation counting can only be approached scientifically if all major factors influencing the count are known. These include collimator length, shape, lead thickness, probe site and angle, and atten-

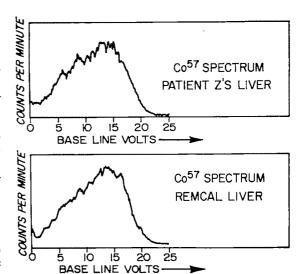


Fig. 5. Co<sup>57</sup> spectrum of patient and Remcal liver using collimator A with sleeve.

uation of body mass. Each factor can be individually assessed, minimized or made constant. It should be quite obvious that the geometric field of a collimator tells

Table II  ${
m CO^{57}}$  count per minute per microcurie detected at remcal liver site from respective organs

	Organ and count/min./µc detected				
Collimator	Spleen	Heart	Lungs	Kidneys	Stomach and Intestines
B and Sleeve	30	0	3	139	81
B No Sleeve	46	0	15	363	210
A and Sleeve	79	29	44	440	239
A No Sleeve	160	71	44 86	964	464
No Collimator and Sleeve	208	76	III	1,070	647
No Collimator No Sleeve	591	224	394	2,697	1,182

Table III

RATIOS OF VARIOUS COMBINATIONS OF COLLIMATORS TO COLLIMATOR B AND SLEEVE (COUNTS DETECTED AT REMCAL LIVER FROM OTHER ORGANS)

Collimator	Spleen	Heart	Lungs	Kidneys	Stomach and Intestines
B and Sleeve B No Sleeve A and Sleeve A No Sleeve No Collimator and Sleeve No Collimator No Sleeve	1.00 1.53 2.63 5.33 6.93 19.70	0 29 71 76 224	1.0 5.0 14.7 28.7 37.0 131.3	1.00 2.61 3.17 6.94 7.70 19.40	1.00 2.59 2.95 5.73 7.99 14.59

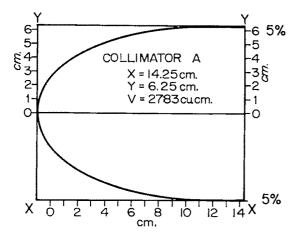


Fig. 6. Parabolic nature and volume analysis of 5 per cent isoresponse curve.

very little as compared to the isoresponse curve. In addition, an isoresponse curve is only valid for a specific energy and a specific collimator or collimators which are identical in all aspects as to length, lead thickness, shape and diameter.

The objective of the studies for which the collimators were designed was the repeated counting of an organ in one subject. A measurement of the organ contents or a comparison of the results, quantitatively, between subjects was not made. The method of volume determination could, however, give some indication of radioactivity content within the volume counted. The per cent fall-off curve for an extended source showed the possible error of quantitatively comparing data between patients. The liver counting sites can be determined, marked and recorded. Further, to eliminate angular error for subsequent counting, a special compass for measuring the angles of the probe in two planes was used (Fig. 4B). These angles can be reproduced for succeeding studies in a subject.

The similarity of the Co<sup>57</sup> spectrum of the patient's liver and the spectrum of Co<sup>57</sup> in the Remcal liver supports the validity of applying data from Remcal to specific studies in patients. Unwanted counts from other organs could be reduced con-

siderably, as shown in Table II and III. From these results, we feel confident that the data obtained are representative of Co<sup>57</sup> in the liver. Further, the counts from other organs detected by these designed collimators should be insignificant, due to the low amount of B<sub>12</sub> usually found in these organs.<sup>1</sup>

The selection between probes A and B was determined by the dose given and the duration of the study. For a study of longer duration, we would use collimator A because of its comparatively higher count/min./µc. We believe that the data obtained by us would be difficult to obtain by means other than those presented here. The plan of design and testing for our study was for Co<sup>57</sup> counting of the human liver; however, the over-all approach could be applied to other situations. The testing method can be applied to collimators presently owned by investigators.

#### SUMMARY

The design and testing of collimators are described and illustrated. The geometric field of the collimator is analyzed in terms of optics. The isoresponse curve is treated as a near parabola and its approximate volume is calculated as a volume of revolution. The count rate obtained during external scintillation counting of organs is shown to be a function of the type of collimator, probe position, probe angle, and bordering and underlying organs. Results show that in long term organ counting studies, data can only be of value when the probe position is geometrically fixed and recorded for subsequent counting. This should be done in the X and Y planes. Results further show that the quantitative comparison of patient data may be unwise.

Radioisotope Service Veterans Administration Hospital Albany, New York 12208

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# CYCLOTRON PRODUCED SHORT-LIVED RADIOACTIVE ISOTOPES\*

By MICHEL M. TER-POGOSSIAN, Ph.D.† st. louis, missouri

MANY radioactive isotopes which are potentially useful for diagnostic purposes decay with half-lives too short to allow their practical use unless the isotopes are generated either in the immediate vicinity or, preferably, within the medical center where they are to be used. These isotopes may be classified in the category of short-lived isotopes. It is impossible to establish on an absolute scale an upper limit for the half-life of a "short-lived" isotope. It appears, however, that radioactive isotopes which decay with a half-life shorter than about 10 hours cannot be practically shipped away from the area where they are generated, and, therefore, in this presentation, 10 hours is selected as the upper limit for the half-life of a short-lived radioactive isotope.

Short-lived radioactive isotopes are particularly useful for diagnostic purposes because of the following reasons:

- (1) The administration of a short-lived radioactive isotope to a patient results in a lower dose of a radiation delivered, for a given activity administered, than if a longer-lived isotope of the same element had been used.
- (2) The short effective half-life exhibited by short-lived radioactive isotopes allows repeated measurements in the same patient.
- (3) Many elements which are potentially useful as tracers in medicine have only short-lived radioactive isotopes.
- (4) The radiation emitted by certain short-lived radioactive isotopes renders them more useful for medical purposes than longer-lived isotopes of the same elements.

The potential usefulness of short-lived radioactive isotopes for medical purposes

was recognized as early as 1944 when Tobias, Lawrence, and their co-workers<sup>19,25</sup> used carbon monoxide labeled with carbon 11 in the study of the elimination of carbon monoxide from the human body. The carbon 11 used in that study was prepared in the Berkeley cyclotron.

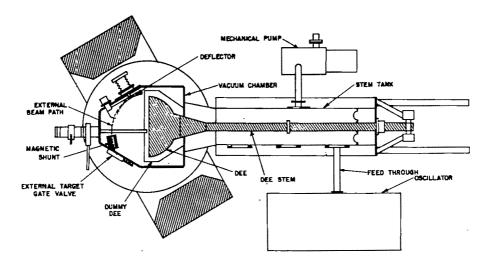
The utilization of short-lived radioactive isotopes in a medical center requires their generation either within the center or in its immediate vicinity.

Short-lived radioactive isotopes can be generated in a medical center by one of two methods: (I) if the desired short-lived radioactive isotope results from the decay of a longer-lived radioactive element, then the short-lived daughter can be prepared by separation from the longer-lived parent usually by chemical means. This method is commonly referred to as "milking" a "radioactive cow." (2) The second method consists in generating the isotope in a more conventional manner by means of nuclear reactions induced either in reactors or by means of accelerators, such as cyclotrons.

The preparation of a short-lived radioactive isotope by chemical separation from a longer-lived parent by the "milking" of a "radioactive cow" is a method particularly appealing in medical applications because it requires a relatively modest apparatus, and several short-lived radioactive isotopes useful for diagnostic purposes are prepared by this method. Such is the ease for technetium 99m, gallium 68, strontium 87m and several others. 7,8,9,18,80 Unfortunately, this simple method allows the preparation of only a small number of isotopes, and most of the other short-lived radioactive elements useful in medicine must be prepared by nuclear reactions either by means

† Professor of Radiation Physics, The Washington University School of Medicine, St. Louis, Missouri.

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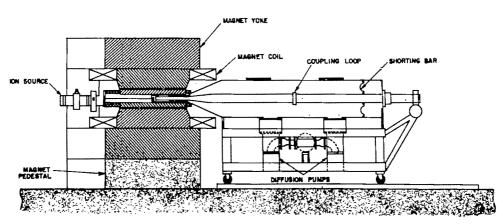


Fig. 1. Plan and elevation of the 33 inch cyclotron installed in the Barnard Hospital, Washington University Medical Center. (Courtesy Allis-Chalmers Co.)

of a reactor or by an accelerator. The majority of the short-lived radioactive isotopes which are particularly useful for medical purposes happen to be of the neutron deficient type, and, therefore, they can be practically prepared only by means of positive ion accelerators. It should be noted that positive ion accelerators are also capable of producing fast or slow neutron fluxes and, therefore, these machines are suitable for the production of any desired radioactive isotope.

For the above reasons, and in spite of the many advantages offered by nuclear reactors over accelerators, 20 positive ion accelerators are preferable for the generation of the short-lived radioactive isotopes

which are useful in medicine. Although many types of positive ion accelerators can be used for the preparation of short-lived radioactive isotopes, at this time it appears that cyclotrons are best suited for this purpose.

For the above reasons, we have decided to install a cyclotron in the Washington University Medical Center with the main purpose of preparing short-lived radioactive isotopes useful for diagnostic purposes.

It may appear at first that a cyclotron is too formidable a machine to be installed in a medical center. In fact, a small size cyclotron quite suitable for the production of short-lived radioactive isotopes is com-

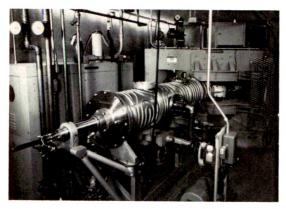


Fig. 2. Rear aspect of the cyclotron. The horizontal cylinder in the center of the picture is the stem tank.

parable in price, in space requirements, and in personnel required for its operation to a conventional 24 mev. betatron.

The cyclotron, which is now in operation in the Washington University Medical Center, was constructed by the Allis-Chalmers Company according to our specifications. This machine is capable of accelerating deuterons to an energy of 6 to 8 mev. with an external beam current of about 50  $\mu$ a. Protons and alpha particles with an energy of 12 to 16 mev. can also be generated in this machine.

Figure 1 shows a schematic diagram of the cyclotron.

This cyclotron is a single dee machine with magnetic pole pieces approximately 33 inches in diameter. The radio frequency oscillator which supplies the power to the dee is usually operated at 10.65 megacycles per second. The magnetic field which bends the accelerated particles into circular orbits has an intensity of about 14,000 gauss. After full acceleration the particles are deflected by means of an electrostatic deflector to which a difference of potential of about 70 kv. is applied. The system is maintained under vacuum by means of mechanical and diffusion pumps operated continuously.

Figure 2 is a photograph of the installed cyclotron showing the stem tank and the vacuum pumps of the magnet. The cyclo-

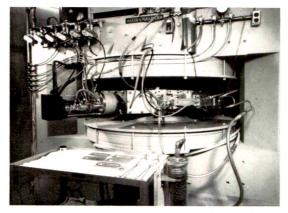


Fig. 3. Front end of the cyclotron showing the chamber used for the irradiation of gases. In the foreground are shown the magnanese dioxide filter and the pump used for the purification and circulation of gases during generation of oxygen 15.

tron is installed in a room approximately 14×25 feet which is partially sunk underground. The total weight of the unit is approximately 25 tons.

Figure 3 shows the output end of the cyclotron. To the left is the supporting structure for the ion source which provides the particles to be accelerated, and the structure to the right is a probe which can be introduced into the apparatus either for measuring the beam or for the irradiation of samples within the vacuum chamber. In most instances, however, the irradiation of samples is accomplished outside the cham-



Fig. 4. Septum-deflector structure used in deflecting the accelerated positive ions from their circular trajectory for the extraction of the cyclotron beam.

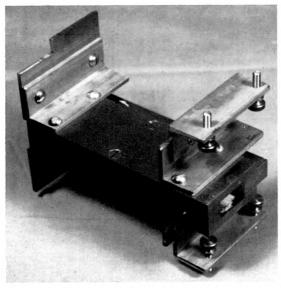


Fig. 5. Magnetic channel used to shunt the magnetic field in the cyclotron for the extraction of the beam.

ber by bringing the beam of accelerated particles out of the vacuum through an aluminum window.

Figures 4 and 5 show various components of the cyclotron.

A great number of short-lived radioactive isotopes potentially useful in medicine can be prepared in the described cyclotron. At this time it is our opinion that the most important ones of these isotopes are oxygen 15, carbon 11 and nitrogen 13. Oxygen 15 decays with a half-life of about 122 seconds with the emission of 1.73 mev. positrons. We are preparing oxygen 15 by the bombardment of nitrogen by means of cyclotron accelerated deuterons. For most medical applications the simplest target material to be used is air which is bombarded at normal temperature and pressure. Figure 6 shows a simplified diagram of

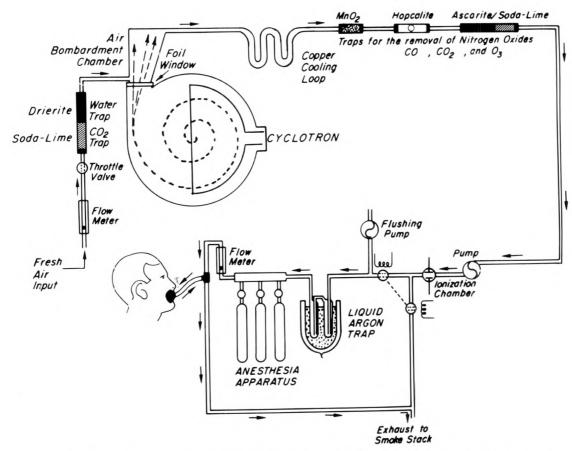


Fig. 6. Schematic diagram of the system for the generation, purification, and utilization of oxygen 15.

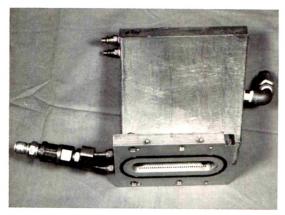


Fig. 7. Irradiation chamber used in the preparation of oxygen 15.

this system used for the preparation of air tagged with oxygen 15.

Figures 7 and 8 show the irradiation chamber which is used in the preparation of oxygen 15.

Oxygen 15 is an isotope particularly useful in biology and medicine for three reasons: (1) Because of the importance of oxygen in metabolic processes, it is desirable to be able to trace this element by means of a radioactive isotope; (2) in spite of its short half-life, oxygen 15 is the longest-lived radioactive isotope of this element; and (3) the emission by oxygen 15 of positrons renders this isotope particularly useful because of the ease of its localization by means of the annihilation radiation emitted when positrons interact with matter. The short half-life of oxygen 15 reduces drastically its value in metabolic studies; however, many aspects of the transport of oxygen in the living system are so rapid that their study is not appreciably hindered by the short half-life of oxygen 15, and we have found this isotope to be extremely useful.

Oxygen 15 has been used extensively in various laboratories as a tracer for oxygen, carbon monoxide, carbon dioxide and water. 1-6,18,19,21-28 Various medical and biologic studies such as (1) the study of the metabolism of oxygen in normal and abnormal structures, (2) the study of pulmonary function, (3) the quantitation of emphysema, and (4) the determination of

the adequacy of oxygen supply to extremities have been carried out with oxygen 15. It should be noted that most of this work has been carried out to this date at the Hammersmith Hospital in London, England.

Carbon II is a radioactive isotope which decays with a half-life of about 20 minutes with the emission of about 1.0 mev. positrons.15,17 This isotope can be prepared in a cyclotron by the deuteron bombardment of boron 11.11,16 After irradiation of boron, radioactive carbon can be extracted from the target in the form of labeled carbon monoxide.11,14 The particular usefulness of carbon II as a tracer in medicine in contrast to carbon 14 is due to the fact that carbon II can be traced in vivo by means of the annihilation radiation emitted subsequent to the annihilation of the positrons emitted by this isotope. Carbon 11 labeled carbon monoxide has been used in studying the fate of inspired carbon monoxide, 12,25 and in the study of pulmonary function.14 In many instances the usefulness of carbon 11 is limited because of its short half-life. It is probable, however, that in certain cases this limitation can be lifted by using the recoil energy of the carbon II for labeling purposes.29

Nitrogen 13 is a radioactive isotope

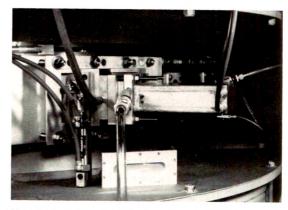


Fig. 8. Attachment of the irradiation chamber shown in Figure 7 to the exit port of the cyclotron. The plate at the bottom of the figure is a one-thousandths of an inch thick aluminum window through which the cyclotron beam escapes the main vacuum chamber and penetrates into the irradiation chamber.

which decays with a half-life of about 10 minutes with the emission of 1.2 mev. positrons.15 This isotope can be prepared in a cyclotron by bombarding boron 10 with alpha particles.14,16 The nitrogen atoms formed in the target can be extracted either in the form of nitrogen gas or they can be used to label NO or N2O. Nitrogen 13 is the longest-lived radioactive isotope of nitrogen, and it is also the only radioactive tracer of nitrogen which can be practically used in biology and medicine. Because of the great importance of this gas in anesthesiology, it is probable that this isotope will find a number of applications in medical studies, although, to this date, none has been extensively described.

#### CONCLUSIONS

It is outside the scope of this short presentation to give a general study of the various radioactive isotopes useful in medicine, which can be prepared in a cyclotron. In addition to the 3 isotopes described above, there are many others.

It should be noted we also have found that the cyclotron may be useful in the preparation of longer-lived radioactive isotopes, such as sodium 24 and potassium 42, which, under certain circumstances of experimentation, are difficult to obtain rapidly from usual suppliers.

It appears that a cyclotron is such a useful adjunct to a medical center, where nuclear medicine is practiced extensively, that in the near future many medical centers will be equipped with these accelerators.

The Washington University School of Medicine 510 South Kingshighway St. Louis 10, Missouri

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## COMPARATIVE STUDY OF EFFECTS OF LASER AND/OR IONIZING RADIATION THERAPY ON EXPERIMENTAL OR HUMAN MALIGNANT TUMORS\*

By PAUL E. McGUFF, M.D., Ph.D. (Surg.),† LEONARD S. GOTTLIEB, M.D.,‡ ISAO KATAYAMA, M.D.,\$ and CHARLES K. LEVY, Ph.D.¶

BOSTON, MASSACHUSETTS

ASER is an acronym for light amplifi-L cation by the stimulated emission of radiation. A laser is an electronic device that utilizes the stimulation of high energy atoms for amplifying a beam of light (Fig. 1). Exceedingly powerful energy densities and other unusual special properties are afforded by the intensely coherent almost completely parallel beams of light.4 Laser is vastly different from roentgen-ray or gamma radiation. Principally, laser energy is non-ionizing unlike roentgen-ray radiation; and also laser can produce tremendously high flux densities. If we compare the wave length of therapeutic roentgen rays with ruby laser, the roentgen rays are very short, indeed from 1.0 to 0.0001 Å compared with the ruby laser wave length of 6,943 Å or 0.7 micron. Laser energy presents a new potential method in the treatment of certain malignant tumors in that the finely focused laser beam will cause progressive regression and ultimate dissolution of an entire tumor rather than just the small area of exposure to the laser radiation and with almost no damage to the surrounding tissues because of laser's almost surgical selectivity for certain malignancy.7

Initially, in ruby laser operation, capacitor banks are charged with electric energy to produce an intense, short light flash from powerful xenon lamps. Chromium atoms in the ruby rod, whose end faces are optically flat and highly silvered, absorb and reradiate energy (fluoresce). A part of

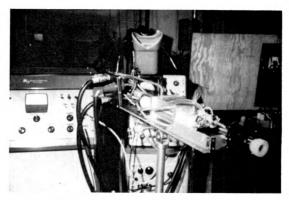


Fig. 1. High energy ruby laser. Water cooled high repetition rate type. (Photo courtesy of Maser Optics, Inc.)

this fluorescent radiation is reflected back and forth within the ruby crystalline rod being amplified at each pass, and laser energy is emitted from the distal end of the ruby rod as a collimated beam of monochromatic coherent light at 6,943 Å. This all takes place in a few milliseconds.

A comparative study of the effectiveness of ruby laser energy treatment with roent-gen-ray irradiation was begun in January, 1964 on adenocarcinomas of human origin transplanted into hamster cheek pouches. Six hamsters with cheek pouch tumors were treated with laser energy, 214 joules/tumor, and another similar 6 hamsters were subjected to 1,000 r which was chosen arbitrarily and was found to be inhibitory to the everted cheek pouch tumors with the remainder of the body shielded. Six hamsters with tumors were treated with

† Director and Chief Surgeon, Laser Medical Research Foundation, Boston, Massachusetts. ‡ Associate Director, Mallory Institute of Pathology, Boston City Hospital, Boston, Massachusetts.

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Surgical Pathology Fellow, Chief Resident, Mallory Institute of Pathology, Boston City Hospital, Boston, Massachusetts.

¶ Director of Radiobiology, Department of Biology, Boston University, Boston, Massachusetts.

 $T_{ABLE\ I}$  summary of comparative effects of laser and/or ionizing radiation therapy on experimental adenocarcinoma

	Laser Treated	Roentgen-Ray Treated	Combined Laser- Roentgen-Rays	Control
No. of Hamsters	6	6	6	6
Laser Dosage	average 214 joule/tumor		average 217 joule/tumor	
Roentgen-Ray Dosage			1,000 r per tumor with body shield	

Single air dose of 150 kv. roentgen rays, target skin distance 25 cm. Rate 123 r/min.,  $\frac{1}{4}$  mm. aluminum filter. Exposed area 1.5-2.0 cm.

combined laser-roentgen-ray therapy and there were 6 control animals (Table 1). Each series of hamsters was treated similarly in follow-up examinations. One animal was chosen by random selection from each group at weekly intervals for 6 weeks. The cheek pouch was grossly examined, photographed, and then excised and sent for histologic study. Measurements of all the tumors were made as one parameter of the experiment: before, and at weekly intervals after the various treatments. A comparative tumor volumetric determination study was made to compare the 4 groups.

The total original volume sum of the tumors in each group was compared with the total volume sum of the tumors at

weekly cheek pouch excision. Results were significant and the following: the laser treated group decreased the most—75.6 per cent in volume. The laser-roentgen-ray therapy group decreased 47.8 per cent in volume. The roentgen-ray treated group increased 40.9 per cent in volume and the control group increased 83.8 per cent in volume (Table II).

The control group showed twice as much increase in tumor size as the roentgen-ray therapy group, but neither of these 2 groups showed any tumor cell destruction upon histologic examination. The laser group showed both gross and microscopic cure in the fifth and sixth week specimens. The laser-roentgen-ray therapy group showed no tumor cells observed upon histo-

TABLE II
RESULTS

		Laser Treated	Roentgen-Ray Treated	Combined Laser- Roentgen-Rays	Control
Week	I	Showed progressive	Increased tumor	*	Greatly increased
	2	regression of tumor	growth weekly	*	tumor growth weekly
	3			Grossly cured*	
	4			Grossly cured*	
	5	Cured grossly*		*	
	6	Cured grossly*		Grossly cured*	
Volum	e	-75.6%	+40.9%	-47.8%	+83.8%

<sup>\*</sup> No viable tumor cells.



Fig. 2. Adenocarcinoma of human origin. Pre laser appearance.

logic examination from the first week on to the sixth week specimens.

In summary then: volumetric determinations demonstrated a 75.6 per cent decrease for the laser group compared with a 47.8 per cent decrease for the combined laser-roentgen-ray therapy group. The laser group showed two tumors grossly and microscopically cured. The combined laserroentgen-ray group showed 3 tumors grossly cured but all 6 specimens were microscopically negative, although with less resorption of residual volume of necrosis than the laser group (Fig. 2 through 9). From prior experience with this tumor, if all 6 lased tumors had been allowed to go to completion of observation of 6 weeks, all the tumors would have been grossly resorbed and microscopically cured.6

In subsequent studies other groups of



Fig. 3. Adenocarcinoma of human origin. Post laser day 35. Note large ulceration.



Fig. 4. Adenocarcinoma of human origin. Post roentgen-ray day 35. A dose of 1,000 r had an inhibitory effect on the growth of this tumor.

hamsters with tumors were given from 500 to 5,000 r of roentgen-ray radiation alone. There were groups of hamsters with tumors which received 3,000 r plus laser and 500 r plus laser and other groups received varying amounts of laser energy. One group received laser radiation after oxygen administration.

Is there a synergistic action between laser and roentgen-ray radiation? We believe that there is one. We had found that there was an inhibitory action on this human type adenocarcinoma when 1,000 r of ionizing radiation was given (see Table 11, comparing volume of tumor in the roentgen-ray treated group with that of control group). The roentgen-ray treated tumor increased in volume 40.9 per cent compared with an increase in volume of 83.8 per cent in the control group. It was also known



Fig. 5. Adenocarcinoma of human origin. Post laser-roentgen-ray day 35. Only 3 small areas of necrosis are seen.



Fig. 6. Adenocarcinoma of human origin. Post control day 35. Tumor is firm and viable.

from our prior experimentation that it required over 200 joules of laser energy to cure one of these experimental tumors. Hence, it was elected to halve the inhibitory dose of 1,000 r to 500 r and also treat these same tumors with only 125 joules of laser energy radiation as nearly simultaneously as possible. Thus, if we cured any of the tumors, knowing that 500 r alone and even 1,000 r would not cure them, or that less than 200 joules of laser energy alone would not cure them, we would have proved a synergistic action of laser and roentgen-ray radiation. The experimental results showed that one-half of the hamsters were cured of their tumors and that one-half were not. This will be reported in greater detail at a later date.

Rounds<sup>11</sup> recently found that exposure of a line of human adenocarcinoma cells to



Fig. 7. Tumor has undergone complete dissolution by post laser day 42. No tumor cells seen upon histologic examination.



Fig. 8. Appearance at post laser-roentgen-ray day 42. Only rosette of mucosa remains. No viable tumor cells seen upon histologic examination.

approximately 20 joules/centimeter<sup>2</sup> of laser energy, followed by 250 r gamma radiation from a cobalt 60 source, reduced the population to 52.1 per cent of control values by the fourth post-treatment day. Gamma radiation of 250 r dosage alone depressed the population to 77.4 per cent of controls.

Helsper and Sharp<sup>3</sup> recently communicated to us the case of a patient who had an adenocarcinoma of the breast with an area of ulcerated skin metastases which they treated with two methods of therapy. A single large area was treated with multiple bursts of ruby laser radiation and then a similar area was treated with a single 450 r dose of ionizing radiation from a cobalt 60 source immediately followed by multiple firings of ruby laser energy. Helsper and Sharp felt that clinically there



Fig. 9. Adenocarcinoma of human origin. Post control day 42. Tumor is firm and viable. Tumor cells were seen upon histologic examination.

was definitely a greater effect in the combined cobalt 60 plus laser irradiated area.

Almost 6 months ago, we used laser energy on a basal cell carcinoma of the nose. It was necessary to use laser energy a second time. A recent biopsy showed no carcinoma remaining upon histologic examination and there was no gross evidence of existing carcinoma. The tumoricidal effect of laser energy on human malignant tumors has been reported by us previously<sup>5-8</sup> and by others.<sup>1,2</sup>

### CONCLUSIONS

Laser radiation is unique because it has a selective effect upon certain malignant tumors in that it causes their progressive regression and eventual complete dissolution while it causes only slight injury to normal tissues excluding the retina. Although thermal effects have been carefully observed, recorded, and analyzed by us, 7,9,10 the mechanism of laser energy radiation on certain malignant tumors is still unsolved. The principal biologic effect of laser radiation on malignant tumors may or may not be that of heat alone. Enzymes may be altered or lose their specificity and exceedingly high electrical fields may cause the breaking of molecular bonds.

Dissolution of certain tumors varies, and depends upon factors such as the absorption capability of the tumor, ratio of dose to tumor volume, and the laser radiation dosage and energy density used. Deeper lesions require a surgical exposure for laser application, unless they can be approached by utilization of endoscopes or fiberoptic instruments.

Laser and ionizing radiations in this one experimental adenocarcinoma of human origin group were synergistic. Laser radiation alone may cure certain tumors, and ionizing radiation alone may cure certain tumors, but their combined use may have interesting and rewarding future possibilities.

Paul E. McGuff, M.D. 25 Circle Drive Weston, Massachusetts 02193

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# TOWARDS THE IDEAL USE OF THE "OXYGEN EFFECT" IN RADIOTHERAPY

### THE RECIPROCAL OXYGENATED ANOXIC METHOD

By E. A. WRIGHT,\* G. M. HAHN,† and R. E. STEELE‡ LONDON, ENGLAND

THE existence of anoxic cells in tumors has been predicted by Thomlinson and Gray<sup>8</sup> and supported by the work of Powers and Tolmach.<sup>5</sup>

Because anoxic tumor cells may be 3 times as resistant to the effects of x-ray and other low LET radiation compared with oxygenated cells, great efforts have been made to oxygenate these cells by subjecting patients to several atmospheres of oxygen before and during radiotherapy.8

The alternative idea of protecting the normal tissues from the effects of radiation by anoxia and irradiating the tumor with higher doses has also been advocated. This would be theoretically equally effective compared with the "oxygen method." However, no adequate trial of the anoxic method has yet been published although the technical difficulties of making normal tissue surrounding a peripheral tumor anoxic are not formidable.

It is relatively simple to make a small animal anoxic for brief periods and carry out irradiation in a few seconds, 11 but there are doubts as to whether this method can be effectively used for larger mammals.

Both the "oxygen" method and the "anoxic" method aim at bringing the normal and tumor tissues into parity with regard to radiosensitivity. The ideal, however, would be to oxygenate the tumor tissues while at the same time making the normal tissue anoxic and resistant.

To achieve this aim, it is suggested that use is made of the necrotic tumor masses so frequently found in human tumors. These masses are usually separated from normal tissue by a thin "rim" or "shell" of tumor cells approximately 150  $\mu$  thick.<sup>8</sup>

While only the innermost layer of tumor cells is thought to be anoxic, it has been shown that even a few per cent of anoxic tumor cells are of a disproportionate importance considered from the point of view of curability of a tumor mass.<sup>4</sup> The masses of necrotic tissue are very variable in size and shape but are frequently more than 1.0 cm. in diameter and it is assumed that they do not respire.

The method proposed is to slowly saturate these necrotic masses with oxygen by making the patient breathe oxygen at an optimum pressure for an optimum time then quickly render the normal tissues anoxic. Humans can only breathe high pressures of pure oxygen for limited periods. It is, therefore, not a simple problem to determine the optimum time and pressure of oxygen needed to arrive at a desirable level of oxygen tension in these necrotic masses. Indeed, a complex schedule might be most suitable, such as atmospheric pressure of pure oxygen for a prolonged time and followed by higher pressures for a relatively short period. When the necrotic masses are fully saturated with oxygen by passive diffusion to the highest practicable level, the normal tissues are rendered anoxic rapidly. Hypoxia of normal tissues may be attained by breathing an inert gas such as nitrous oxide, hydrogen or nitrogen, by occluding the blood supply or by compression of the tissue. There will then follow a limited period of time when the diffusion gradients of oxygen tension will be reversed, the tumor tissue will be oxygenated and the normal tissue will be anoxic. The maximum possible theoretic benefit from this procedure is that the previously

<sup>\*</sup> St. Mary's Hospital Medical School, London, England.

<sup>†</sup> Stanford University School of Medicine, Palo Alto, California.

<sup>‡</sup> Hewlett-Packard Laboratories, Palo Alto, California.

anoxic tumor cells would be *relatively* 9 times as sensitive as before. The success of this method would be dependent on the presence of a mass of necrotic tissue, the practical limits to the oxygen tensions attainable and the time factors involved.

For any trial of radiotherapy, one would ideally need a number of cases of tumors with a relatively short prognosis, not presently well treated by radiotherapy or surgery, diagnosable at an early stage and if possible not forming metastases. For this reciprocal oxygenated-anoxic method, one would require tumors prone to necrosis and occurring in a normal tissue with a high respiration rate known to become anoxic readily. The brain and its tumors might fulfill these requirements.

In principle, the idea is sound and by intuitive guesswork it would seem that

there are situations where the method could be successful, at least when considered in qualitative terms. However, any animal experiments on the radiosensitivity of the brain to doses in the therapeutic range are of necessity long term, as the effects do not appear for many months (for example, in rabbits?) and may extend to years in humans.¹ We have thus attempted to construct various physical and mathematical models to serve as guides to animal experiments and to aid in forming an opinion as to the ultimate feasibility for radiotherapy.

### THE HYDRAULIC MODEL

One simple working model consisted of a series of tall transparent plastic cells representing tumor cells and a large adjacent cell representing a necrotic area (Fig. 1).

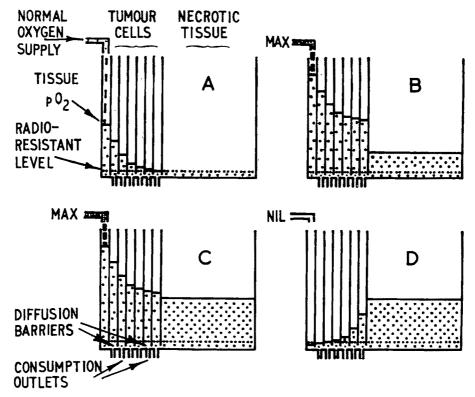


Fig. 1. Diagrams of the hydraulic model representing oxygen tension gradients in tumors under various conditions. (A) Normal state. The innermost "cell" next to the necrotic tissue is hypoxic and radioresistant. (B) pO<sub>2</sub> of blood is raised. The necrotic tissue, acting as a reservoir, begins to fill. (C) Steady state, finally reached when pO<sub>2</sub> in innermost cell equals pO<sub>2</sub> in necrotic tissue. (D) Oxygen supply is suddenly cut off. For a short period the normal oxygen gradient is reversed. The cell that is most likely to remain oxygenated is the one that was previously, under normal conditions, the least oxygenated.

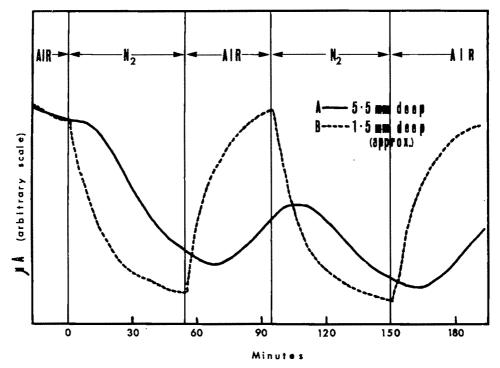


Fig. 2. The recordings from two electrodes embedded in agar spheres while saline saturated with air or nitrogen was streamed past. The scales of the two recordings were adjusted so that they were equal at the first change from air to nitrogen. This was done because one electrode gave slightly but proportionately smaller readings under equal conditions.

Uniform small holes between the cells represented the diffusion barrier and the height of fluid in the cells represented the oxygen tension in the cells. Oxygen consumption was represented by sucking fluid out of the cells through a small hole by a negative pressure that was relatively high compared with the height of the fluid in the cells. Under these circumstances fluid introduced into the "outermost cell" (i.e., away from the necrotic cell) would partly "diffuse" through the hole into the adjacent cell and partly be "consumed" (by suction). By adjusting the rate of flow, "consumption" and "diffusion" factors, a situation probably bearing some similarity to that of the natural tumor was obtained. This model was used to demonstrate the principle that the necrotic tissue could be slowly saturated with oxygen and that by cutting off the delivery of oxygen the gradients of oxygen tension could be reversed.9

### OXYGEN TENSION IN AGAR MODELS

Another model consisted of masses of agar in which were embedded small bare tipped platinum electrodes so that the oxygen tension in the agar was measured polarographically. The largest sphere of agar used was I.I cm. in diameter and electrodes were placed approximately 1, 2, 3 and 5.5 mm. deep. Saline solution in equilibrium with air or nitrogen was rapidly streamed past the spheres. Although the results are only semiquantitative, it can be said that the most deeply placed electrode responded very slowly to changes in the gas tension in the surrounding medium (Fig. 2). When the gas tension (of oxygen) in the surrounding medium was changed from approximately 140 mm. Hg to near zero, little or no change was observed for approximately 10 minutes at the deep site. Even after 60 minutes the change was only two-thirds complete. The response time of electrodes not surrounded by agar but free in the fluid was only a few seconds with this particular arrangement. These results bear a resemblance to the time factors calculated by using a mathematical model, which is next to be discussed.

### THE MATHEMATICAL MODEL

For the purpose of this study, a number of assumptions and obvious over-simplications had to be made. Many of the basic constants have been borrowed from Thomlinson and Gray. With regard to the diffusion constant for tissue, it is assumed that live tissue and necrotic tissue are similar. This appears reasonable although it is known that necrotic tumor tissue varies widely in consistency from semifluid to caseous masses.

Gray's estimate of  $\mathcal{Q}_{o_2}$  on Warburg's findings are used although the certainty of these figures is not known. Tumor oxygen consumption for a group of isolated viable cells free of stroma might be higher than for tumor masses which include many tissues other than tumor. An adequate  $\mathcal{Q}_{o_2}$  for brain tumors has not been found.

All tumors are irregular in shape and mostly show a very complex structure of healthy, damaged and necrotic tissue. However, it was thought that the sphere represented a closer approximation than the cylinder for this situation.

The idealized tumor is shown in Figure 3. The sphere bounded by the surface  $r=r_1$  represents the necrotic central mass. The volume between  $r=r_1$  and  $r=r_2$  is occupied by the viable tumor tissue. The surrounding tissue  $(r>r_2)$  is nonmalignant. The oxygen partial pressure, p, under normal breathing conditions is zero in the central mass, and rises inside the tumor tissue until it reaches its normal value  $p_0$  at  $r=r_2$ . Its behavior is governed by the diffusion equations (Rashevski, page 29):

$$D\nabla^2 p - \mathcal{Q}_{O_2} = \frac{\delta p}{\delta t}, \qquad r \geq r_1;$$
 
$$D\nabla^2 p = \frac{\delta p}{\delta t}, \qquad r < r_1. \qquad (1)$$

The steady state solution of (1) is given by Rashevski<sup>6</sup> (page 39):

$$p_{si} = \frac{1.31 \times 10^{-6}}{6} r^{2} + \frac{1.31 \times 10^{-6}}{3} \frac{r_{1}^{3}}{r} - \frac{1.31 \times 10^{-6}}{2} r_{1}^{2}.$$
 (2)

The boundary conditions are obeyed providing that  $r_2$  is a solution to:

$$\frac{r_2^3}{6} + \left(1.31 \times 10^{-6} p_0 - \frac{r_1^2}{2}\right) r_2 + \frac{r_1^3}{3} = 0. \quad (3)$$

Equation 3 establishes the thickness of the tumor rim. Its solution is plotted for two values of  $p_o$  in Figure 4 ( $p_o$  is the oxygen partial pressure in the region  $r > r_2$ ).

The patient is now placed in a high pressure oxygen chamber, causing a rise in partial pressure to a value  $p_1$  in the non-malignant areas. As a result, the oxygen pressure in the tumor rises until a new steady state is reached given by:

$$Pst_1 = Psto + P_1 - P_o. \tag{4}$$

The transient behavior can also be calculated using the techniques described in Carslaw and Jaeger<sup>2</sup> (p. 233):

$$p_{t} = -\sum_{n=0}^{\infty} \frac{2r_{2}[p_{1} - p_{o}]}{n\pi r} \sin\left(\frac{n\pi r}{r_{2}}\right)$$
$$\cdot e^{-nDr^{2}t}/r_{2}^{2}. \tag{5}$$

### NORMAL TISSUE

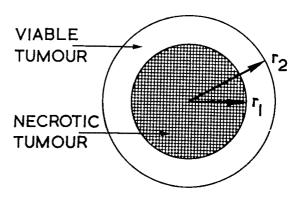


Fig. 3. Idealized spherical tumor mass.

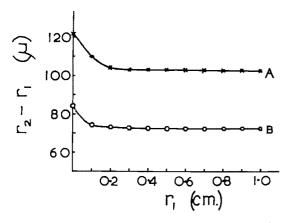


Fig. 4. The thickness of the viable tumor rim in relation to the radius of the central necrotic mass for two different oxygen pressures at the surface of the viable tumor tissue.

The time to reach 90 per cent of steady state value at the center of the necrotic mass (i.e., at r=0) is approximately:

$$t_{90}(r=0) \cong \frac{5.3r_2}{D\pi^2} \cdot \tag{6}$$

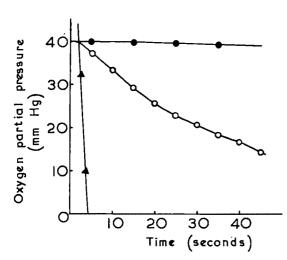


Fig. 5. Time dependence of oxygen partial pressure. Tumor size 1 cm. diameter, partial pressure at t=0, 40 mm. Hg  $(r< r_1)$ , 80 mm. Hg  $(r>r_2)$ . Zero time is time at which oxygen no longer reaches tumor surface.

O<sub>2</sub> partial pressure at center of necrotic tissue (r=0)

O<sub>2</sub> partial pressure at center of viable rim  $(r=r_1+r_2)/2$ 

O<sub>2</sub> partial pressure at considerable distance from tumor (r=2r<sub>1</sub>)

For  $r=\frac{1}{2}$  cm.,  $D=2.6\times 10^{-7}$  cm.<sup>2</sup>/sec. 90 per cent of the final value is reached after 90 minutes, a value consistent with experimental data.

In order to reduce the oxygen tension in nonmalignant tissue to anoxic values, the external oxygen supply is removed. The oxygen partial pressure, of course, still obeys equations (1). The new initial conditions are given by equation (4). A closed solution to this problem could not be obtained. Direct integrations of equations (1) on the Stanford Burroughs 5500 computer\* yielded the results shown in Figures 5 and 6. Figure 5 illustrates the time behavior of the partial pressure of oxygen for various points inside and outside the tumor. Figure 6 shows the spatial variations of oxygen partial pressure at fixed times. In these graphs t=0 refers to the time at which oxygen is no longer supplied to the tumor

\* We are indebted to Dr. Donald Fisher of the Stanford Computer Center for programming the solution.

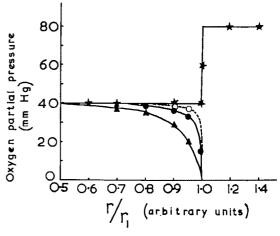


Fig. 6. Spatial distribution of oxygen partial pressure in vicinity of tumor rim, at zero time,

$$P_0 = 40 \text{ mm. Hg } (r = < r_1)$$
  
 $P_1 = 80 \text{ mm. Hg } (r > r_2)$ 

Zero seconds after oxygen ceases
to reach tumor
30 seconds after oxygen ceases
to reach tumor
60 seconds after oxygen ceases
to reach tumor

120 seconds after oxygen ceases

to reach tumor



surroundings. Obviously, this time point may be different from the time at which the patient's breathing conditions are changed.

#### SUMMARY

The following conclusions may be drawn from the mathematical results:

- 1. The time for a sufficient amount of oxygen to diffuse into the necrotic volume is of the order of 1 hour or less.
- 2. Once oxygen supply to the tissue is interrupted, normal metabolism causes the oxygen tension to drop precipitously within a few seconds, protecting the nonmalignant tissue.
- 3. Most of the tumor tissue is kept oxygenated by outward diffusion from the necrotic "reservoir" for a period of 60 to 90 seconds.

These 3 approaches using different types of models all indicate that the necrotic tissue of tumors might be used as reservoirs for oxygen and, further, that adjacent tumor cells could be kept oxygenated and radiosensitive for a short period while the normal tissues could be protected by hypoxia.

We recognize that our assumptions oversimplify the situation usually found in patients with tumors but suggest that there is some basis for continued efforts to devise means of testing this potentially dramatic approach.

E. A. Wright
Department of Pathology
St. Mary's Hospital Medical School
London, W.2, England

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# SOME POTENTIAL APPLICATIONS OF THE "OXYGEN EFFECT" TO RADIOTHERAPY\*

By E. A. WRIGHT LONDON, ENGLAND

THERE is good evidence for the belief that there are anoxic and therefore radioresistant cells in many tumors. 19 It follows from this that it is desirable to overcome this relative radioresistance of tumor cells.

This article will be concerned with methods of attaining this aim although there are certain areas of uncertainty, such as the value and effects of fractionation, which will not be dealt with.

The most direct way to raise the radiosensitivity of these anoxic cells is to make the patient breathe oxygen at high pressures. High pressures are necessary because the hemoglobin in the red blood cells is almost fully saturated with oxygen in the lungs and oxygen is only sparingly soluble in plasma at normal pressures. However, the use of hyperbaric oxygen requires special apparatus and techniques. It may, therefore, be useful to list and comment on some of the other possible ways that could be used to circumvent the disadvantageous presence of anoxic cells in tumors. Some of the suggestions are common knowledge; some have only been discussed at meetings or privately. It is hoped that the following list and comments will lead to further work and the trial of some of the possible methods.

### LIST OF POSSIBLE METHODS

- A. Increasing the oxygen tension in tumors
  - 1. High pressure of oxygen in respired gas
  - 2. Intra-arterial infusion of hydrogen peroxide
  - 3. Cooling and other methods to reduce oxygen consumption by tissues
- B. Reducing the oxygen tension in normal tissues

- 1. Generalized hypoxia by breathing an inert gas
- 2. Local hypoxia by compression or ligature
- 3. Deep hypothermia (near o°C.)
- C. Avoidance of the "oxygen effect" by using radiation of high LET
  - 1. Fast neutrons (producing protons)
  - 2. Negative  $\pi$  mesons (producing alpha particles)
- D. Physiologic combinations and other methods
  - Reducing distance between capillary and anoxic or necrotic tumor before conventional or "oxygen" radiotherapy
    - (a) Bleeding followed by autotransfusion
    - (b) Prolonged breathing at reduced pO<sub>2</sub> or induction of partial HbCO levels
  - 2. Changing to an acid pH of the blood
  - 3. Use of necrotic areas as oxygen reservoirs: the reciprocal oxygen/anoxic method.

### NOTES AND COMMENTS ON METHODS

### A. INCREASING THE OXYGEN TENSION IN TUMORS

1. High pressure of oxygen. This method has been most widely used.<sup>4</sup> The patient is given pure oxygen to breathe at increased pressures up to 3 atmospheres or more. This allows enough oxygen to dissolve in the plasma to make it likely that the tumors will be better oxygenated. The technical difficulties of irradiation under these circumstances have led to a change in the fractionation regimen and this has made comparison of the results with conventional therapy uncertain. The theoretic aspects of this method have been fully discussed.<sup>10</sup>

<sup>\*</sup> From the Department of Pathology, St. Mary's Hospital Medical School, London, England.

Also to be considered is the contraction of blood vessels when presented with high tensions of O<sub>3</sub>, which has been postulated for the brain<sup>5</sup> and clearly demonstrated in the retina.<sup>1</sup>

- 2. Intra-arterial infusion of hydrogen peroxide. This method has been explored by Mallams et al. 16 There is evidence that the oxygen tension can be raised in tissues by this method. Hydrogen peroxide in saline solution is slowly infused into an artery. The catalase of red blood cells will liberate oxygen. If the infusion rate is judged correctly, it seems that bubbling can be avoided and the pO<sub>2</sub> in the capillaries and, therefore, tissues can be significantly raised.
- 3. Cooling and other methods of increasing tissue oxygen tension. Although experimental evidence demonstrates that the overall oxygenation and radiosensitivity of animals under deep hypothermia (i.e., temperatures near o°C.) are reduced, 18 lesser degrees of hypothermia may cause a rise in oxygen tension of tissues. This is probably because mild cooling allows the tissue requirements for oxygen to be lowered to a greater extent than the reduction in oxygen supply, but, when deep hypothermia is applied, respiratory movements cease and the supply of oxygen is completely stopped. The slow consumption of oxygen by the tissues continues and renders the tissue anoxic.3 Bloch and his colleagues2 showed that, when patients with cerebral tumors were subjected to light hypothermia, their brains became very sensitive to relatively small doses (200 r) of radiation. This reaction, which appeared to be due to cerebral edema, occurred a few hours after irradiation. Although this method seems to have very serious disadvantages for the central nervous system, it is a promising idea for other sites in the body. The complexity and variability of the tissue reactions to cold are well illustrated by observing the exposed skin of people in cold weather. Some areas are pink and presumably well oxygenated, other areas are blue, and possibly hypoxic, while other areas

are white, and although ischemic, there is no obvious indication as to the state of their oxygenation. Further, the sensitive basal cells may be at a different oxygen tension to the underlying tissues because of their different metabolic rate or because of diffusion through the surface.

Another aspect that has not been fully explored is the abolition of the usual constriction of blood vessels by cold by using the now well established sympathetic blocking agents of the alpha type.

Other methods of reducing the consumption of oxygen by tissues are possible. Cyanide, by local perfusion, is theoretically possible. This would combine with the cytochrome-c and prevent the oxygen being used. There are also now several other agents that block the Krebs cycle and may have similar, longer lasting and less hazardous actions.

#### B. ANOXIA

If the normal tissues can be made fully radioresistant by hypoxia, then the oxygen tension in the tumor can be ignored. (If there is any oxygen left in the tumor, this is all to the good.) It should be pointed out that the arguments for the presence of hypoxic cells in tumor tissue can also be applied to normal tissses and that the normal cells most distant from their capillaries will be at a lower pO<sub>2</sub> than the rest. In the case of the pia of the brain, this has been well demonstrated by Davies and Bronk in 1957.8 As survival of a normal tissue can be achieved by "saving" only a few per cent of cells (in some organs like the skin), it follows that only a very minor proportion of tissue need be fully anoxic to show major degrees of radioresistance. Thus, a normal tissue can survive almost as though the whole tissue were anoxic even though some oxygenated blood is passing through its capillaries. However, each tissue must be considered separately because of widely differing anatomic and physiologic factors.

If normal tissues are fully oxygenated normally and anoxia can be induced in them, a greatly increased dose, taking full advantage of the oxygen enhancement ratio (OER) can be given. However, it has been shown that some normal tissues are not normally fully oxygenated and thus there may be danger in increasing the dose by the full OER.<sup>14</sup>

- 1. Generalized hypoxia can easily be achieved in small animals sufficient to give a protective factor of more than 2.7,15,23,24 This method of therapy has been suggested, 23,24 but not yet applied.
- 2. Local hypoxia can be produced by ligatures and compression cuffs or injecting vasoconstrictor drugs. There has been a trial of this method by van den Brenk et al.<sup>22</sup> in 1962. Van ven Brenk and his colleagues carefully considered the theoretic and practical aspects and report favorably on the treatment of cases. Care must clearly be taken to confirm that small amounts of oxygenated blood do not seep past a cuff via nutrient arteries to bones, particularly if any part of an anoxic tissue is allowed to cool.<sup>4</sup>
- 3. Deep hypothermia is known to produce hypoxia and radioresistance in small animals but whether this is paralleled in larger animals and man remains to be seen. In particular, it is possible that some parts, such as skin, might retain sufficient oxygen to be radiosensitive even if color changes suggested anoxia. Again, deep hypothermia as a method of protecting normal tissues during radiotherapy has not been tried.
- 4. Another possibility is to maintain the tissues at a high temperature while causing only a partial reduction in the blood supply. Perhaps in any method, depending on the consumption of oxygen by normal tissues, it would be advisable to ensure that an adequate temperature was maintained.

### C. AVOIDANCE OF THE "OXYGEN EFFECT"

Radiations with a high LET generally show a smaller oxygen effect. Alpha particles from polonium have a very high LET and an oxygen effect approaching one. However, although charged particles of low energy have very high LETs, they also have very limited powers of penetration in tissues and are, therefore, very limited in their application.

Fast neutrons. Fast neutrons, being uncharged, penetrate deeply into tissues and expend most of their energy by producing recoil protons from the hydrogen atoms present in tissues. The LET of protons produced by cyclotron neutrons of mean energy 6 mev. is relatively high but oxygen enhancement ratios of 1.7 have been recorded. This is much lower than the usual figure found for 250 kv. x-ray, 2.5 to 3.0, and, therefore, appreciable benefit is expected.<sup>8</sup>

Negative  $\pi$  mesons. Another (at present theoretic method) is the use of  $\pi$  mesons. These should produce alpha particles and heavier ions with extremely high LET and only negligible OER.<sup>25</sup>

### D. PHYSIOLOGIC COMBINATIONS AND OTHER METHODS

- 1. Procedures aimed at reducing the distance between capillary and necrotic tissue. Severe anemia reduces radiosensitivity.<sup>18</sup> It is reasonable to suggest that this is due to the production of anoxic cells because of the anemia. It also follows that, in time, if a patient changes from the normal to the anemic state, the maximum distance between a capillary and a necrotic tumor cell must also be reduced. This is because the oxygen carrying power of the blood is reduced and the respiration rate of cells does not vary with oxygen tension until extremely low levels are reached. It thus follows that the oxygen diffusing through a layer of tumor cells adjacent to a capillary will have consumed all the oxygen in a shorter distance. Tumor cells can survive in the anoxic state for several days<sup>20</sup> so that the rim of viable tissue will not decrease immediately. Two possible ways of achieving this reduction are as follows.
- (a) Production of anemia by bleeding with subsequent autotransfusion. (Discussed with Dr. Y. Maruyama.<sup>17</sup>) Blood could be withdrawn several times during 1 week to produce a severe anemia. The red blood cells, if need be, could be separated

and the plasma readministered. The red blood cells or blood could be stored with little deterioration for 2 to 3 weeks, particularly if adenine is added. During this period, depending on the health and nutrition of the subject, there would be some replacement of the red blood cell population, but, at an optimum moment, the stored blood could be returned and conventional radiotherapy carried out. By serendipity, a slightly raised hemoglobin might also be achieved. This method has the disadvantage that the shrinkage of the tumor zone induced by anemia has not been proved but has the considerable attraction of utilizing well established simple techniques regularly carried out in modern clinical practice.

- (b) An alternative way of achieving the same end would be to either reduce the pO<sub>2</sub> of inspired air for a prolonged period, say 2 to 3 weeks, or to limit the oxygen carrying capacity of the hemoglobin by producing controlled amounts of HbCO in the blood. Both of these methods are even simpler than the bleeding idea but involve novel techniques or apparatus.
- 2. Changing the pH of blood. Variations in the pH of the blood significantly change the hemoglobin dissociation curve. Lowering the pH causes a shift to the right, i.e., for a given pO<sub>2</sub> more oxygen is given up. It thus follows that because mixed venous blood is usually still appreciably oxygenated, a lower pH will cause a higher pO<sub>2</sub> in tissues. Temporary recoverable changes to very low pH levels can be achieved in the experimental animal by inducing CO<sub>2</sub> narcosis (Nunn, 1960). Experimental evidence is required to demonstrate that a change to an acid pH does, in fact, induce a raised tissue pO<sub>2</sub>.
- 3. The use of necrotic areas in tumors as reservoirs of oxygen. Many human malignant tumors show areas of necrosis which range in size from microscopic zones to vast masses many centimeters across. It is suggested that these areas are used as depots of oxygen. Necrotic tissue does not respire and, therefore, by raising the pO<sub>2</sub> of the respired gas these areas will slowly be-

come saturated with oxygen. If now the normal tissues are made suddenly anoxic and radioresistant, the oxygen will diffuse out into the tumor. The cells most likely to be oxygenated for the longest time by this method will be the very cells that, under normal conditions, are anoxic. A variety of mathematical and physical models have been made to demonstrate this reciprocal oxygen-anoxic method and the results suggest that it would probably take 90 minutes to saturate a necrotic zone I cm. in diameter 90 per cent, and that, for 90 seconds after the normal tissues had become anoxic, the tumor cells would remain oxygenated.12 If this ideal state were achieved, the previously anoxic tumor cells would now be relatively of times as radiosensitive as before.

### CONCLUSION

It seems extremely probable that one or more of these methods, either alone or in combination, will find a place in radiotherapy, either generally or in specific areas. Although the basic principle appears simple, the practical therapeutic application is often difficult and complex. It would appear that quite minor deficiencies in technique may viciate the hoped for benefit. There thus seems a danger that any particular method may become discredited by a few early failures if adequate ability in the use of new techniques is not fully established and sufficient controls are not used. Some of the great difficulties of assessing new radiotherapeutic methods are the very long times that must elapse before an improvement over other methods can be demonstrated, and the relatively small numbers of comparable cases that a single therapeutist encounters for his trials. Thus, if any of these methods are considered for trial, it is most desirable that sufficient cases are available and that the trial is designed in such a way that a real difference will be revealed, if present. The most likely way of achieving this seems to be for many centers to cooperate in a properly controlled trial, using one of the well established statistical methods of sequential analysis.

Department of Pathology St. Mary's Hospital Medical School London, W. 2, England

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# RESULTS FROM TOURNIQUET ANOXIA AND HYPERBARIC OXYGEN TECHNIQUES COMBINED WITH MEGAVOLTAGE TREATMENT OF SARCOMAS OF BONE AND SOFT TISSUES\*

By H. A. S. van den BRENK, M.B., M.S. (Melb.), F.R.C.S. (Eng.), D.T.R., F.C.R.A.; R. C. KERR, M.B., B.S. (Melb.), M.C.R.A.; J. P. MADIGAN, M.D. (Melb.), F.R.A.C.P., D.T.R., F.C.R.A.; N. M. CASS, M.B., B.S. (Melb.), F.F.A.R.C.S., F.F.A.R.A.C.S.; and WENDY RICHTER, M.I.R.

MELBOURNE, AUSTRALIA

PROGNOSIS in sarcomas of bone and soft tissues is usually poor, largely owing to a high incidence of metastases to lungs, bones and other organs. Metastases are ultimately responsible for the death of most patients. Dissemination of tumor cells occurs early in the evolution of the disease but the subsequent rates of growth of the metastases to produce clinical manifestations varies greatly, being very rapid in certain type tumors but delayed for years in others. Since no adequate therapy exists capable of curing such metastatic disease, for a majority of patients all treatments are essentially palliative from the outset, irrespective of whether radical measures such as amputation or high dose roentgen radiation are adopted in treating the primary condition. The onset of metastases cannot be predicted with certainty and/or varies from weeks or months in most juvenile osteosarcomas to as much as several years in other conditions (certain soft tissue sarcomas, synoviomas and chondrosarcomas). This variation in prognosis becomes of importance in designing treatment for the primary condition, according to type of tumor, its more likely pattern of behavior, the age and sex of the patient, occupation, etc. While an adequate surgical amputation of the limb appears the logical primary treatment in most cases, one hesitates to adopt this policy routinely as a first measure. Thus, in highly malignant juvenile bone sarcomas most patients die from metastases within 12

months. Similarly, early death occurs in Paget's sarcoma. In other less progressive conditions, in which metastases may not appear for a few years but, nevertheless, ultimately cause death in the majority, one would wish to control the tumor and preserve the limb in a useful, pain free condition for as long as possible. Furthermore, in more highly malignant tumors, some clinical evidence appears to suggest that an ablation of the primary tumor (e.g., by amputation) precipitates an earlier onset of metastatic growth and shortens survival time. Various unproven mechanisms have been proposed from time to time to explain this effect, such as the systemic dissemination of tumor cells by operative interference, hormonal and immunologic mechanisms, an unknown balance of growth between the primary tumor and its metastases, etc. This has led to various preoperative radiation techniques being employed in sarcomas, aimed at sterilizing the neoplasm in situ, partially or wholly, followed by amputation. In soft tissue sarcomas, a local surgical removal is more often attempted, followed by prophylactic postoperative radiotherapy, or sometimes radiotherapy is delayed until such time as a recurrence appears.

A modified "preoperative" regimen of radiotherapy was adopted and practiced at the Royal Melbourne Hospital and Peter MacCallum Clinic, Melbourne by Scott<sup>12</sup> in sarcomas of bone and, to a lesser extent, soft tissue neoplasms over a period of years.

<sup>\*</sup> From the Radiobiological and Hyperbaric Oxygen Research Units, Cancer Institute Board, Melbourne, Australia.

This scheme attempted to delay the selection of patients for amputation for 12 to 18 months by administering repeated prolonged courses of fractionated roentgen radiation during this time to control the growth of the primary tumor. An elective amputation was recommended if no metastases were evident when this period had elapsed on the assumption that (a) such tumors had not metastasized or (b) that occult metastases had spontaneously resolved, due to some indirect tumor-host mechanism. Limbs received large volume orthovoltage irradiation, usually doses of 6,000 to 7,000 rads being administered initially over 10 weeks as daily fractions and, subsequently, repeated at 6 month intervals but with doses reduced to 4,000 to 5,000 rads given at the same daily dose rate. If the tumor failed to respond and regress after irradiation, the limb was amputated forthwith. Amputation was also performed if radionecrosis or severe deformity developed or if pain resulted which caused sufficient discomfort to warrant this measure. This policy seemed logical in preventing a significant number of amputations in those patients who developed early metastases resulting in early death and in reserving amputation for patients who appeared potentially "cured" of the disease. The radiation administered produced quite gross changes, and of sufficient severity to limit the time the limb remained useful and pain free to relatively short periods of 1 to 2 years or less. Not infrequently, some discomfort persisted or worsened during the 12 to 18 month waiting period, calling for amputation. Naturally, the patients spent a large proportion of their remaining lifetime visiting the radiotherapy department for treatment. A retrospective survey of cases of bone sarcoma so treated and registered with the Peter MacCallum Clinic, made by two of us (J. P. Madigan and H. A. S. van den Brenk), showed that their survival was not significantly better or worse than that of comparable material treated by various methods in various centers elsewhere. A

comparison is shown in Table 1 for medullary sarcoma of bone (including Paget's sarcoma), in which the Peter MacCallum figures compiled in 1958 are compared with those of Thomson and Turner-Warwick16 from the Middlesex Hospital London, a series published by Geschickter and Copeland<sup>7</sup> and published results of Prevo,<sup>11</sup> Cade, Platt<sup>10</sup> and Evans and Schreiber. It is difficult to make strict comparisons in view of clinicopathologic difficulties experienced in the classification of bone tumors, each author using his own criteria for selection. However, these various results appear sufficiently clear-cut to conclude that there was no significant difference in over-all survival for the various centers adopting a variety of surgical and radiotherapeutic methods alone or in combination, if allowance is made for a uniformly poorer prognosis (irrespective of treatment) in juvenile bone sarcoma and in Paget's sarcoma, and a much better prognosis in many types of chondrosarcoma. However, it did appear from the Peter MacCallum Clinic results based on Scott's techniques that early survival (6 to 12 months) may have been somewhat improved while late (5 year) survival was not significantly better or worse than that for methods employing immediate or early amputation, with or without the addition of radiotherapy. It was also quite clear from this analysis that the practice recommended by Cade<sup>2</sup> of high dose irradiation followed by early amputation was not significant in improving upon the survival rate obtained by amputation without radiotherapy. The Peter MacCallum Clinic results also failed to show that long delay of amputation caused a spontaneous resolution of occult metastases but improved early survival could be related to a delay in the progression and growth of metas-

As a result of this analysis and many reports in the literature suggesting that ablation of a primary sarcoma of bone plays little part in modifying ultimate prognosis in most cases, it was decided

that the primary aim should be to preserve optimum integrity and function of limbs for as long as possible, employing the more conservative modality of radiotherapy. This depended largely on whether a better response of tumors to irradiation could be achieved and result in a high percentage of tumor control and eradication. With the advent of megavoltage radiation, the "skin sparing" effects and reduction of dose differentially absorbed in bone for this quality seemed a step towards this goal. Even more promising seemed to be the introduction of

"oxygen effect" in modifying radiosensitivity, following the experimental studies of Gray et al.8 and Wright and Howard-Flanders.22 These results led to the clinical studies pioneered by Churchill-Davidson et al.,5 employing hyperbaric oxygen and tourniquet anoxia to differentially modify tumor and tissue radiosensitivity, respec-

Our initial experience with tourniquet anoxia in radiotherapy of sarcomas of the extremities and the techniques used has been published<sup>20</sup> and further experience

TABLE I SURVIVAL STATISTICS FOR MEDULLARY SARCOMA OF BONE EXCLUDING "ROUND CELL"-RETICULUM CELL TUMORS AND EWING'S TUMORS (VARIOUS AUTHORS)

Authors	Disease Classification*	Surviving Fraction (per cent) after Treatment					
		3 months	6 months	12 months	18 months	3 years	5 years†
Geschickter and Copeland <sup>7</sup> (1949)	Juvenile Osteosclerotic Osteosarcoma	62/87 (71)‡	47/87 (54)	32/87 (37)	24/87 (28)	20/87 (23)	20/87 (23)
	Osteolytic Osteosarcoma	31/49 (63)	23/49 (47)	13/49 (26)	9/49 (18)	6/49 (12)	6/49 (12)
	Primary Chondrosarcoma	55/60 (92)	42/60 (70)	26/60 (43)	20/60 (33)	9/60 (15)	9/60 (15)
	Osteosclerotic Osteosarcoma	41/55 (75)	39/55 (71)	30/55 (55)	19/55 (35)	14/60 (25)	14/60 (25)
	Osteolytic Osteosarcoma	42/64 (66)	32/64 (50)	24/64 (37)	18/64 (28)	10/64 (16)	10/64 (16)
	Primary Chondrosarcoma	35/40 (88)	27/40 (68)	19/40 (48)	15/40 (38)	8/40 (20)	8/40 (20)
	All Juvenile Cases All Adult Cases Total Cases	148/196 (76) 118/159 (74) 266/355 (74)	112/196 (57) 98/159 (62) 210/255 (60)	71/196 (30) 73/159 (46) 144/355 (41)	53/196 (27) 52/159 (33) 105/355 (30)	35/196 (17) 32/159 (20) 67/355 (19)	35/196 (17) 32/159 (20) 67/355 (19)
revo <sup>11</sup> (1950)	"Osteogenic" Sarcoma 24 Cases Chondromyxosarcoma 16 Cases Fibrosarcoma 10 Cases	41/50 (82)	33/50 (66)	23/50 (46)	13/50 (26)	10/50 (20)	7/101 (7)
Thomson and Turner-Warwick <sup>16</sup> (1955)	Osteoblastic Sarcoma (Including Paget's sarcoma)	****	22/32 (69)	7/32 (22)	5/32 (15)	4/32 (13)	2/31 (7)
	Chondrogarcoma (Grade 3)		6/10 (6c)	3/10 (30)		1/10 (10)	1/10 (10)
	Combined		28/42 (67)	10/42 (24)		5/42 (12)	3/41 (8)
Peter MacCallum linic, Melbourne van den Brenk and Madigan (unpub- ished survey 1958)	Medullary Sarcoma of Bone (including Paget's sarcoma)	41/43 (95)	36/43 (84)	23/43 (54)	12/42 (29)	8/41 (29)	7/41 (12)
Cade <sup>2</sup> (1955) teleradium series)	Osteogenic Sarcoma (including chondro- sarcoma)	-	_	Namenal	4	_	10/84 (12)
latt <sup>10</sup> (1951)	Osteogenic Sarcoma (including chondro- myxosarcoma)					32/120 (27)	19/120 (16)
Evans and chreibers (1957)	Osteogenic Sarcoma (juvenile)		-	7/15 (47)	6/15 (40)	3/15 (20)	3/15 (20)

<sup>\*</sup> Paget's sarcoma excluded in series of Platt, and Evans and Schreiber, not specified in the reports of Geschickter and Copeland, Cade, and Prevo, not included in the two series of Thomson and Turner-Warwick and van den Brenk and Madigan in relatively similar proportions.

† Details of 5 year survivors according to histologic types:

\*\*Geschichter and Copeland\*\*—osteosarcoma (50 cases) and chondrosarcoma (17 cases).

\*\*Preson\*\*—osteosarcoma (2 cases), chondrosarcoma (4 cases), fibrosarcoma (17 case).

\*\*Thomson sud Tarner-Warwick\*\*—osteosarcoma (2 cases), chondrosarcoma (17 case).

\*\*pas den Brenk and Madigan\*\*—osteosarcoma (4 cases), chondrosarcoma (2 cases), spindle cell sarcoma (1 case).

\*\*Cade\*\*—osteosarcoma (8 cases), chondrosarcoma (2 cases).

\*\*Plati\*\*—osteosarcoma (6 cases), chondrosarcoma (13 cases).

\*\*Plati\*\*—osteosarcoma (6 cases), chondrosarcoma (13 cases).

\*\*Esons and Schreiber\*\*—not specified (juvenile "osteogenic" sarcoma—3 cases).

†\*In parenthesis\*\*—per cent of cases.

with this technique was also reported by Suit.<sup>16</sup> In this paper current results and techniques used in this Unit are reported and discussed.

### THE PRODUCTION OF TISSUE ANOXIA

The relationship of tissue and cellular radiosensitivity to extracellular oxygen concentration [O<sub>2</sub>] is given by the Alper and Howard-Flanders equation:

$$\frac{S-S_N}{S_N}=(m-1)\frac{[O_2]}{[O_2]+K},$$

where K and m are constants (K=5-10) $\mu$ M O<sub>2</sub>/liter and m = 2.74, respectively). To reduce tissue radiosensitivity to a minimum value, oxygen tensions must be reduced to near zero values, relatively small concentrations of oxygen (<5 mm. Hg) being sufficient to increase radiosensitivity substantially above minimum (anaerobic) values. From a practical point of view, if radical therapeutic doses are to be prescribed with anoxic conditions prevailing in the tissues, conventional doses used under aerobic conditions must be multiplied by an oxygen effect factor of the order 2-3. Should such modified doses be administered to inadequately deoxygenated tissues, necrosis and severe tissue damage may be confidently predicted.

In the production of tissue anoxia for radiotherapeutic purposes, techniques are at present limited to the extremities in which a tourniquet is used to temporarily cut off the blood supply and produce tissue anoxia. However, tourniquet techniques produce inherent complications which must be considered. Although various workers recommend and use different types of tourniquet, in our own investigations we have preferred the Esmarch type elastic rubber bandage applied circumferentially to the limb proximal to the site to be irradiated. Two complications may arise: (a) In tumors of the thigh, it is often difficult to apply a tourniquet sufficiently proximal to the tumor to allow irradiation of adequate tissue margins proximal to the tumor, particularly in massive soft tissue tumors of the thigh. In such circumstances radiation is sometimes delivered to skin covered by the tourniquet. This strip of skin receives a peak dose with megavoltage (4 mev.) qualities and shows more severe skin reactions than the remainder of the irradiated skin. Frequently, such tumors are now preferentially treated in hyperbaric oxygen at 4 ATA. Thus, tumors of the proximal third of the thigh, hip or pelvis are unsuitable for tourniquet anoxia and are treated with the patient pressurized in oxygen at 4 ATA in a pressure vessel<sup>17</sup> and doses modified accordingly.<sup>21</sup> The application of a tourniquet not infrequently produces a tourniquet palsy. In 2 of the first 29 cases treated in this Unit, tourniquet palsies were produced. One resulted after the third treatment in the lower limb of a 38 year old male. This palsy disappeared within 3 months. The second was produced in the upper limb of a 17 year old male after the third treatment, but disappeared within I month. Tourniquet palsies were clearly related to nerve trauma produced by local pressure of the tourniquet and not to the duration or completeness of limb anoxia. Two further tourniquet palsies, both in upper limbs, have since been produced. It appears that the application of a tourniquet to the slender upper limb may be more dangerous in this respect than in the lower limb. However, the nerve injury appears related to a neuropraxis and is similar to that produced by postural damage and stretching under anesthesia. Regeneration and recovery of function have occurred in all our cases.

The efficacy of a tourniquet in producing a sufficiently complete anoxia of normal tissues is of major importance. This problem has caused us some apprehension and has been responsible for what may be considered overzealous efforts on our part. Thus, our techniques have been largely guided by tissue oxygen tension and other measurements of blood flow, with time after tourniquet application to ensure that adequate time is allowed for the production

of anoxia before the tissues are exposed to radiation.<sup>20</sup> The tourniquet is applied for 30 minutes before the radiation exposures are given. Furthermore, during this period of progressive anoxia, the limb is heated in an electric blanket to increase oxygen consumption. Also, electrodes are applied to the musculature of the tissue volume to be irradiated and this musculature is vigorously tetanized until complete fatigue sets in, also with a view to accelerating oxygen consumption and the production of more complete tissue anoxia. We believe these measures to be much more effective in contributing to general tissue anoxia than that of reducing the direct diffusion of oxygen through the rather thick human skin from without. In small laboratory animals (mice), the diffusion of oxygen through thin skin may be of importance. Indeed, pressurized oxygen surrounding a mouse's leg has been shown to significantly modify tissue anoxia distal to a tourniquet if this animal is placed in a hyperbaric oxygen chamber. 19 Levels of radiosensitivity comparable to those in air without tourniquet constriction were recorded in this experiment. However, in the experiments of Suit<sup>13</sup> with human skin, the oxygen enhancement factor of 2.5 in air obtained for tourniquet anoxia suggests that the thickness of human skin probably prevents significant amounts of oxygen diffusing from the outer air to the basal layers of the epithelium and subcutaneous tissues.

Recent experiments using radioiodinated human serum albumin I<sup>131</sup>-HSA, administered intravenously as 0.6 mc doses in patients with 1 or 2 tourniquets applied to the lower limb, have shown that appreciable amounts of blood continue to enter a limb distal to a tourniquet. This flow apparently occurs by way of nutrient vessels entering the incompressible bone shaft, proximal to the tourniquet, and being transmitted along medullary vascular channels and spaces, to leave the bone and enter soft tissues distal to the site of soft tissue compression. However, it appears that the amount of blood bypassing the

tourniquet is limited and significant amounts rarely reach the ankle region, even if a single high tourniquet has been applied. This amount of oxygen conveyed to tissues distal to a tourniquet appears to be rapidly exhausted by metabolism. The radiation doses administered to large volumes of tissue in the 2 patients submitted to this investigation  $(3 \times 2,500)$  rads and  $6 \times 1,857$  rads modal dose in 4 and 5 weeks, respectively) subsequently produced minimal tissue damage. In these 2 cases (an osteosarcoma of the lower end of femur in a male, aged 14 years, and a rhabdomyosarcoma in the thigh of a 65 year old male), regression of tumor was produced and maintained for 12 months after irradiation. The limbs have remained pain free, with only slight skin pigmentation, minimal tissue atrophy and unimpaired function.

Nevertheless, these results indicate that a poorly applied tourniquet may be dangerous, and lead to a false sense of security in respect to doses tolerated by normal tissues.

Anesthesia. In our experience, heavily sedated but conscious patients do not tolerate the discomfort resulting from the application of tourniquets to arrest blood flow in limbs. Anesthesia is also required to immobilize the patient for mock up, field alignment and treatment. All our patients receive premedication and intravenous pentobarbital sodium-morphine anesthesia and preparation as described by Cass³ for hyperbaric oxygen treatments. However, myringotomies and intubation are omitted and a simple oral airway is inserted during treatment.

### TOURNIQUET ANOXIA

In this Unit, the prescription of radiation doses in both hypoxic and hyperbaric oxygen conditions is based on a policy which aims to: (a) reduce the number of fractions; (b) calculate cumulative dose and number of fractions from parameters of cell radiosensitivity provided by the available experimental data; and (c) space

fractions to allow repopulation of normal tissues and recovery to occur to optimum levels.

This policy may be considered unrealistic from a clinical point of view since the relevant quantitative clinical data which are available are rather fragmentary and as other biologic factors of an uncertain nature, which are often emphasized by clinicians, are largely ignored. However, our own clinical experience over the vears with fractionation dose regimens in air, in high pressure oxygen and in anoxia, coupled with laboratory studies, retrospective clinical surveys and a review of literature, gives us sufficient confidence to rely on this policy in prescribing doses and particularly in the investigation of fractionation in clinical studies.

Experience of tolerance of oxygenated normal tissues to irradiation suggests that reactions and damage in most normal epithelial surfaces and connective tissues are acceptable for a cumulative dose (D) divided into f equal fractions to give a cell surviving fraction  $n/n_o$  of the order  $10^{-8}$  for a  $D_o=130$  rads, an extrapolation value of m=4, and derived from the multihit equation for mammalian cell survival:

$$n/n_o = 1 - (1 - e^{-D/D_o})^m$$

A maximum oxygen enhancement factor of 2.7, according to the Alper and Howard-Flanders equation is used.

The policy of calculating and prescribing doses and fractions is qualified by the following limitations based on both experimental and clinical studies:

- (a) The degree of cellular depopulation and damage to normal tissues resulting from single doses in excess of 1,000 rads (oxygenated) is excessive, the remaining viable cell fraction  $(n/n_o \simeq 10^{-3})$  being too small to *effectively* initiate normal tissue repopulation, migration and repair—particularly in epithelia and blood vessels.
- (b) For larger fractions (500 increasing to 1,000 rads oxygenated) proportionately longer times must intervene between treatments for a maximum cellular repopula-

tion, normal tissue recovery and regeneration to occur. Experiments with rat skin showed, however, that a delay of 14 days for 1,000 rad fractions produced maximum available recovery and that for smaller doses this interval is shortened proportionately. 18 The longer this delay, the greater is the risk that a significant cellular repopulation of the tumor will result, as shown by experimental studies.19 Indeed, 14 day spacings for 1,000 rad fractions delivered in hyperbaric oxygen to human mouth and throat tumors appear to allow repopulation of tumors, and sterilization rates were reduced as compared to 7 day spacings.21

This policy, therefore, provides for the administration of fractions in the range 500-1,000 rads (oxygenated) or 1,350-2,700 rads (anoxic), respectively, to give an  $n/n_a$  not in excess of approximately 10-8, with spacings of 3-4 days to 7-14 days for both conditions. The size of the fractions and the number of fractions (f) for a course of treatment are strictly determined by the  $n/n_a$  value prescribed in terms of modal dose values in tissues.

Table II shows doses used in tourniquet anoxia treatments with 4 mev. roentgen rays, expressed as mean or modal tumor doses.

These dose-fractionation schedules have resulted in excellent tissue tolerance in a majority of patients, with the execption of

$$6 \times 2,350 \binom{+63}{-70}$$

rads delivered over days 0-17 to opposing

Table II

Doses and fractionation used in anoxia treatments with 4 MeV. Roentgen Rays

and the second and the second and the second as the second	
$3\times2,000$ rads	(days 0, 7, 21)
$3 \times 2,500-2,700 \text{ rads}$	(days 0, 14, 28)
2×3,360 rads	(days 0, 14)
$6 \times 1,500 \text{ rads}$	$(days \circ -35)$
$6\times1,600$ rads	$(days \circ -35)$
$6\times2,350$ rads	(days 0−17)*

<sup>\*</sup> Exceeded tissue tolerance.

9×30 cm. fields in a male patient, aged 23 years, with an osteosarcoma of the lower left femur. In this patient the tumor had destroyed a 20 cm. length of lower femur and the medial meniscus of the knee joint had been previously removed by a surgeon mistaking the diagnosis. Before treatment, pain, swelling and flexion deformity were present. The irradiation resulted in regression of the tumor and evidence of bone repair, but the limb developed progressive flexion deformity and intermittent pain with recurrent effusions into the joint. Pulmonary metastases were demonstrated 5 months after irradiation and were largely responsible for the decision not to amputate the limb, the patient remaining ambulatory without tumor recurrence but requiring strong analysics to reduce discomfort from the limb.

In tumors of the thigh, where skin was irradiated through the tourniquet to receive a peak dose on the surface, a surface dose of  $3 \times 2,700$  rads produced moist desquamation with delayed healing of skin. In tumors of the lower limb, similar peak doses received by a segment of skin over the tendo achillis through opposing fields exceeded tissue tolerance, and in I patient (a female, aged 69 years, with a massive fungating reticulum cell sarcoma of the lower leg producing foot drop, and also with gross varicose veins present), a peak dose of  $3\times2,550$  rads (0, 14, 28 days) caused a loss of 7 cm.2 of ankle skin. In another female patient, aged 21 years, with a postoperative residual fibrosarcoma of the ankle, 5 months after receiving

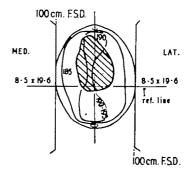
$$3 \times 2.700 \begin{pmatrix} +100 \\ -287 \end{pmatrix}$$

rads modal tumor dose (0, 14, 28 days) producing a peak dose on the skin over the ankle, a knock caused a small patch of skin necrosis over the medial malleolus. An attempted local excision and repair caused spreading necrosis, which was repaired finally with a pedicle graft. However, this patient remains alive and well and free of

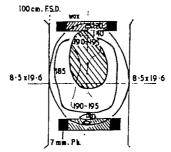
disease with a healed ankle 22 months after irradiation.

The poor tolerance of posterior ankle skin to peak doses has led to the use of shielding, as illustrated in Figure I, in these cases. It also seems clear that lower limbs with pre-existing varicose veins, varicose ulcers and edema often became more swollen after irradiation delivered to the thigh—a complication which has necessitated amputation in 2 cases, in both of which no residual tumor was present in the irradiated zone.

Skin Dose and Build Up. In sarcomas of soft tissue, an incomplete excision may be proven or suspected. Such patients may be referred for postoperative roentgen-ray therapy and present without clinical evidence of recurrence, the wound being quite healed and consolidated. In I such case, megavoltage radiation (6×1,875 rads in 3 weeks) was delivered to a single large



Central contour of ankle without Pb. shielding for skin



7 mm. Pb. ALLOWS FOR 66% T.D. BETWEEN PARALLEL STRIPS Central contour of ankle with Pb. shielding incorporated

in wax

F10. 1. Lead shielding used to spare anterior and posterior strips of skin over the ankle for opposing megavoltage fields.

Survival

4/9

2/8

12 months

24 months

767

field under tourniquet anoxia but without skin build up over the scar, the anoxic skin receiving approximately  $6 \times 900$  rads. Recurrent small tumor nodules up to 6 mm. in diameter were noted in the underdosed cutaneous tissue 12 months after irradiation.

This experience suggests that for postoperative irradiations with megavoltage given in cases for suspected tumor residues but in which no tumor is palpable, the skin should be built up with a sufficient thickness of wax or other material to prevent underdose recurrence. Naturally, this also applies to tumors which invade skin and superficial tissues.

#### SARCOMAS OF BONE

The first 15 cases of bone sarcoma treated with 4 mev. roentgen rays delivered under conditions of tourniquet anoxia are summarized in Tables III and IV. In 4 cases metastases were present before treatment. Juvenile tumors (osteosarcoma 6, chondrosarcoma 1, round cell sarcoma 1 and fibrosarcoma 1) were in the majority (9 cases), 5 of these cases dying of distant metastases at 3, 4, 8, 8, and 21 months, respectively, and 4 being alive at 6, II, 19 and 39 months. Of the 4 living cases, 2 were free of metastases at 11 and 19 months with limbs clinically clear of tumor, while the remaining 2, alive at 6

Table III

MEDULLARY SARCOMA OF BONE TREATED BY
TOURNIQUET ANOXIA AND 4 MEV.
ROENTGEN RAYS
15 cases

Juvenile Sarcoma Adult Sarcoma	9 (7 male, 2 female) 6 (3 male, 3 female)
Types	
Osteosarcoma	8
Fibrosarcoma	3
Chondrosarcoma	2
Reticulum/Round Cell Sarcoma	2

### TABLE IV

MEDULLARY SARCOMA OF BONE TREATED BY TOURNIQUET ANOXIA AND 4 MEV.

ROENTGEN RAYS

15 cases

	•	•
Postradiation Recurren	it Growth	
Definite	I case	
Indefinite	3 cases	
No Recurrence or App.	arent Residual Tumor	- 11/15
Clinical Estimate 6-	–39 months	8/15
$(A_6 A_7 A_9 A_{10} A_{11})$	$A_{19} D_{21} A_{29}$	
No tumor at autops	sy or amputation	3/15
Pain Free Limb Funct	ion Post Radiation	10/15
Amputation		2/15
No tumor in both c	ases	
(1 month for patho	logic fracture,	
18 months for varic	ose veins, edema,	
ulceration)		

and 38 months respectively, developed pulmonary metastases. In the second case, a male, aged 19 years, with a fibrosarcoma of the left fibula, recurrent after attempted excision, pulmonary metastases have appeared 3 years after irradiation. The limb remains intact, function is unimpaired and there is no evidence of recurrence. The dose delivered to this case was  $3\times2,000$  rads mean tumor dose on days 0, 7 and 21, to  $5.5\times20$  cm. long fields.

Two of the 6 adult cases (osteosarcoma 2, fibrosarcoma 2, chondrosarcoma 1 and reticulum cell sarcoma 1) died at 11 and 12 months from distant metastases, but both were free of tumor in the irradiated zone, proven at autopsy. The remaining 4 cases are alive at 7, 9, 10 and 26 months, 3 free of metastases, the fourth at 9 months (fibrosarcoma of femur) with pulmonary metastases which were already present before irradiation. The patient alive at 26 months (a female, aged 62 years) had an amputation at 18 months for severe edema precipitated by gross varicose veins producing ulceration distal to the irradiated zone. This limb was also free of tumor and the

only histologic evidence of radiation damage reported at 18 months after

$$3 \times 2,500 \begin{pmatrix} +360 \\ -270 \end{pmatrix}$$

modal tumor dose to 25 cm. long opposing fields was that some "radiation osteitis" was present

This limited experience with tourniquet anoxia in malignant bone tumors compared favorably with previous experience using more conventional small and large fraction techniques in air, and leads to the following conclusions:

- (1) Survival rates appear no better but no worse as might be expected on biologic grounds.
- (2) Tumor clearance rate and control (73 per cent in the tourniquet series) is improved. In the Peter MacCallum Clinic series (Table 1), repeated courses of orthovoltage roentgen radiation totalling from 10,000 to > 20,000 rads were prescribed and produced gross tissue changes which rarely allowed adequate maintenance of limb function beyond 6 to 12 months. The clearance and tumor control rate was approximately 40 per cent in this series (which excluded the round cell—reticulum cell— Ewing's tumor group). In 5 cases reported by Suit<sup>14</sup> and treated in air with 6,000-7,000 rads in 3 to 4 weeks (fractionated, alternate days), I recurrence was noted at 6 months and 4 cases were controlled locally from 3-7 months.
- (3) Damage to normal tissues produced by tourniquet treatments was considerably less and normal function was restored in a majority of those limbs in which gross deformity was absent or other disorders, such as varicose edema, did not complicate the clinical situation.
- (4) A 3 fraction course over 21-28 days to give an  $n/n_0$  value of  $\simeq 10^{-8}$  appears to produce results equal to or better than larger numbers (6) of fractions in respect to tumor clearance rate and control, and normal tissue tolerance. Indeed, we have reverted to 3 fractions of 2,500-2,700 rads delivered in 3-4 weeks under anoxia in the

treatment of these tumors as more expeditious, economical and equally effective.

The high incidence of early metastases in bone sarcomas is illustrated by this series. The incidence is similar in reports of other treatments. For example, Suit, 14 in 11 cases of osteosarcoma treated by a tourniquet technique, reported distant metastases as present or causing death in 9 cases within 12 months of treatment, despite local control of disease in 10 cases over this period of time.

### SOFT TISSUE SARCOMAS

Results in 14 cases treated with 4 mev. roentgen rays under tourniquet anoxia are shown in Tables v and vI. Adult cases predominated. In a majority (9/14 cases) excisional surgery had been attempted. In 4 such cases (3 synovial sarcomas and I neurofibrosarcoma), the excision was incomplete on histologic grounds, and all 4 cases were alive at 10, 13, 22 and 34 months respectively, free of recurrence and metastases.

In the remaining 5 cases (3 fibrosarcomas, 1 synovial sarcoma and 1 melanoma), moderately sized to massive recurrences were present after one or more surgical attempts. Three patients died of metastases at 6, 7 and 19 months, respectively, all with

Table V

SOFT TISSUE SARCOMA TREATED BY TOURNIQUET
ANOXIA AND 4 MEV. ROENTGEN RAYS
14 cases

Juvenile Cases	4 (1 male, 3 female)
Adult	10 (5 male, 5 female)
	00000000
	14
	- A COMMON
Types:	
Fibrosarcoma	6
Synovial Sarcoma	4
Neurofibrosarcoma	1
Liposarcoma	1
Mesenchymoma	1
Melanoma	1
Metastases before Treatment	2/14
Previous Surgery	9/14

Table VI

SOFT TISSUE SARCOMA TREATED BY TOURNIQUET
ANOXIA AND 4 MEV. ROENTGEN RAYS
14 cases

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El minimi de cara menemento en como proporto en como por el como de cara de ca		
Survival Time	12 months	-8/11
	24 months	5/9
Postradiation Recurrence		
Indefinite		4/14
No Evidence of Recurrence of Clinical (6-42 months)	or Residu <mark>al Tum</mark> o	$\frac{r}{7/14}$
Autopsy or amputation		3/14
Functioning Pain Free Lim (3/14 died of metastases ment)		7/11
Necrosis of Skin (peak dose	es of 8,400 rads)	2
Tumor outside Treated Zone	,	3
Amputations		ĭ
Skin Grafts, Excision of Ne	crotic Tumor	2
Death from Metastases		7/14

complete regression of treated tumors. However in I case, a melanoma with massive multiple deposits also present outside the treated zone, residual ulceration of fungating tumors included in the irradiated zone was produced. The remaining 2 cases, both fibrosarcomas, are alive at 21 and 25 months, I with recurrence outside the treated zone and metastases, the other well with no evidence of active or residual disease or distant metastases.

Of the remaining 5 previously untreated cases, I died at 2 months from metastases present before treatment, and I at 14 months from distant metastases. In this latter patient there was no local recurrence, but a necrotic breakdown of a large liposarcoma of the thigh was produced due to softening after irradiation and resulted in a residual sinus which failed to heal. Three cases were alive at 4,6 and 42 months without evidence of local recurrence or metastases.

Experience in this series confirms conclusions reached for bone sarcomas. However, survival appears better in the soft tissue group although early metastases still commonly appear. In this group, local

recurrence in the limb outside the treated zone was seen despite the use of fields which appeared to provide liberal margins of safety. Tumors of the thigh may be too large and too proximally situated to allow for the application of a tourniquet. Recurrence or activity of disease is often difficult to assess in tissues previously subjected to operation and scarring, but in this group of 14 tumors, of which 13 received 2 to 3 large fractions and 1 six fractions, an example of active progressive recurrent growth within the irradiated zone has not occurred so far. Recently, however, 2 examples of active recurrence have occurred within 12 months, 1 in a case of synovial sarcoma and I in a rhabdomyosarcoma, and both were treated with 6 fractions of 1,500 rads in 4 weeks—a dosefractionation prescription now considered unreliable and inferior to  $3 \times 2,500-2,700$ rads in similar over-all time.

### TREATMENT IN HYPERBARIC OXYGEN (HPO<sub>2</sub>)

The survival time in this group consisting of a total of 31 cases of bone and soft tissue sarcomas of the trunk was very poor, the treatment in HPO2 often being given as a palliative measure to reduce the pain and discomfort from massive tumors, frequently recurrent after previous radical surgical and radiation treatments, and in patients in whom metastases were also often present before HPO2 treatments were given. Nevertheless, tumor control and even complete regression was produced by irradiation in hyperbaric oxygen in a majority of cases, and proved well worthy of any extra efforts involved. A majority of cases received 1,000 rad fractions at 7-14 day intervals, the 4 mev. roentgenray treatment being given to anesthetized patients exposed to 4 ATA oxygen in a pressure chamber as previously scribed.17,21

### SARCOMAS OF BONE

The 22 cases receiving treatment in HPO<sub>2</sub> are shown in Table VII.

### TABLE VII

### sarcomas of bone treated by hpo<sub>2</sub> and 4 mev. Roentgen rays (head, trunk, hip or shoulder regions) 22 cases

Paget's Sarcoma (5)	azed 59-89 years
Chondrosarcoma	2
Osteosarcoma	2
Angiosarcoma	I
Radiation Sarcoma (4)	aged 9, 20, 22 and
All spindle cell or cartilage tumors	56 years
Other Sarcomas of Bone (7) Osteo- fibro- and chondro- sarcomas, but no evidence of Paget's disease obtained	<i>aged</i> 18–66 years
Ewing's Sarcoma, Reticulum Cell Sarcoma (3)	aged 14, 19, 23 year
Miscellaneous (3)	

Myeloma of spine

Chordoma of sacrum

Adamantinoma of jaw

(1) Paget's Sarcoma. This is a highly lethal condition. A previous analysis of cases treated in the Peter MacCallum Clinic made by two of us (J.P. Madigan and H.A.S. van den Brenk) showed that most cases died within 6 months of treatment and all before 24 months.

(aged 70 years)

(aged 66 years)

(aged 74 years)

Results with HPO<sub>2</sub>/4 mev. roentgen rays are shown in Table VIII. Survival was no better with this treatment, but good palliation was obtained in 4 cases with relief of pain and tumor regression which seemed superior to that obtained previously by conventional methods. In 1 case, a female, aged 59 years, with a large sarcoma of the calvarium,  $3\times1,\infty$  rads (days 0, 7 and 21) resulted in necrosis of underlying normal cerebral tissues.

(2) Radiation Sarcoma. The 4 cases treated resulted from neoplastic change induced in benign conditions of the face (osteitis fibrosa and lymphangioma) in patients receiving irradiation 6 or more years previously. One case (a female, aged

### TABLE VIII

# PAGET'S SARCOMA TREATED BY HPO; AND 4 MEV. ROENTGEN RAYS 5 Cases

Previous Treatment—3/5			
Metastases Demonstrated before	Treat	ment-	2/5
Doses			-
$2\times1,000$ rads (0, 7 days) in	2 case	S	
3×1,∞ rads (0, 7, 21 days)	in 3	cases	
Survival at 12 Months-1/5 (a.	ll dea	d at 2,	3, 6, 10
and 14 months)			
Marked Persisting Regression			
(2 autopsies performed and	d no	tumor	demon-
strated)			
Causes of Death			
Metastases	(3)		
Arteriosclerosis	(1)		
(cerebral hemorrhage)			
Radiation damage to brain	(I)		

20 years), presented for HPO<sub>2</sub> treatment after unsuccessful roentgen radiation and a complete absence of the lower jaw following its excision, with residual sarcoma infiltrating the upper jaw and base of skull. This residue was irradiated with  $6 \times 5 \infty$  rads in HPO<sub>2</sub> which produced regression but metastases shortened this girl's survival (Table 1x).

(3) Osteo-, Chondro- and Fibro-Sarcoma. In the 7 cases, there was no evidence of Paget's disease; 6 were adults and I a juvenile, a male, aged 18 years, with an osteosarcoma (?metastasis) of the hip following a hindquarter amputation performed 6 months previously for an osteo-

### TABLE IX

RADIATION SARCOMA TREATED BY HPO2 AND
4 MEV. ROENTGEN RAYS
4 Cases

Previous Surgery, or Roentgen-ray Therapy (excluding original irradiation inducing the tumor)—3/4

Doses in HPO<sub>2</sub> 3×8∞ rads (2) 6×5∞ rads (2)

Survival at 12 Months—2/4 (all dead at 5, 11, 15 and 15 months, respectively)

Marked Regression Persisting after Treatment—2/4 (autopsy on 1 case failed to reveal residual disease)
Causes of Death

Local tissue damage ± recurrence (2)

metastasis (2)

sarcoma of the contralateral femur. In this patient, who died 18 months after HPO<sub>2</sub> treatment from metastases in lungs and bones, almost the entire pelvis received  $3 \times 1,000$  rads mean tumor dose. The tumor, which had destroyed most of the acetabulum and pelvic bone and projected to fill the pelvis and cause intractable sciatic pain, regressed with dense calcification. For 12 to 15 months before further metastases developed, the boy remained pain free and was able to use crutches, swim, etc. The irradiated hip remained free of recurrent growth and necrotic or other severe radiation sequelae until the time of his death from pulmonary and spinal metastases. The results for this group are summarized in Table x.

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(4) Ewing's Sarcoma, Reticulum Cell Sarcoma. Only 3 cases received treatment in HPO<sub>2</sub>—2 cases of massive "Ewing's sarcoma" of the pelvis and hip, the third a case of reticulum cell sarcoma recurrent in the chest wall following 5 courses of roentgen-ray therapy and 2 surgical attempts (including a forequarter amputation). The latter recurred after 2×1,000 rads in HPO<sub>2</sub> given with a view to temporary palliation in the presence of distant metastases (Table x1).

Previous experience with this group of tumors treated in air by conventional techniques has produced variable results in terms of response of tumors to radiation,

### TABLE X

OSTEO-, CHONDRO-, AND FIBRO-SARCOMAS TREATED BY HPO2 AND 4 MEV. ROENTGEN RAYS 7 cases

Previous Surgery ± Roentgen-ray Therapy—6/7
Metastases Demonstrated before Treatment—2/7
Doses in HPO<sub>2</sub> 2×1,000 rads (3), 3×1,000 rads (4)
Survival at 12 Months—3/7 (6 dead at 6, 6, 6, 10, 18
and 37 months; 1 alive at 17 months with metastases in lungs)

Marked and Persisting Regression—6/7 (no residual tumor at autopsy in 3 cases)

Causes of Death
Metastases (5)
Recurrence causing paraplegia (1)

### TABLE XI

EWING'S SARCOMA, RETICULUM CELL SARCOMA TREATED BY HPO2 AND 4 MEV. ROENTGEN RAYS 3 Cases

Previous Treatment—Surgery ± Roentgen-ray Therapy—2/3
Survival at 12 Months—0/3 (dead at 6, 8 and 9

Causes of Death-Metastases-3/3

months)

Tumor Response—2 clear at autopsy (both received 3×1,000 rads); I recurrent (received 2×1,000 rads)

some appearing radiosensitive and others radioresistant to doses of 6,000 rads or more fractionated roentgen-ray therapy. In a series of 19 cases of round cell and reticulum cell sarcoma of bone from this clinic treated with orthovoltage roentgen rays, 15/22 survived 12 months, 4/21 surviving 5 years. Results from Westminster Hospital<sup>16</sup> were similar, 13/23 and 2/19 surviving 1 and 5 years, respectively. Thus, as for other medullary sarcomas of bone, less than 20 per cent of cases survive 5 years.

That these tumors may be radioresistant if irradiated under conventional conditions has been our own experience and also that of Suit<sup>14</sup>—an experience which appears to warrant the additional use of HPO<sub>2</sub> or tourniquet anoxia in attempting to improve results of radiation treatment.

- (5) Miscellaneous Bone Tumors (See Table XII for results). In summarizing our experience in these cases of bone tumors treated in 4 ATA oxygen with 4 mev. roentgen rays, it is concluded that:
- (a) Survival was not significantly altered by the treatment, most patients being dead, and only 7/22 (32 per cent) surviving 12 months. This is to be compared with 4/9 survivors reported by Churchill-Davidson<sup>4</sup> for HPO<sub>2</sub> treatments but in cases in which previous treatment had largely been avoided (personal communication), whereas in this series 16/22 (73 per cent) were recurrent after 1 or more radical attempts at treatment by surgery, roentgen-ray therapy or both, with

### TABLE XII

MISCELLANEOUS BONE TUMORS TREATED BY HPO2

AND 4 MEV. ROENTGEN RAYS

3 Cases

- (I) Myeloma of Spine (aged 70 years), died 5 months after 2×1,000 rads from generalized disease
- (II) Chordoma of Sacrum (aged 66 years), died 8 months after 3×1,000 rads (0, 7, 21 days) which produced tumor breakdown and necrosis of sacrum. Metastases present
- (III) Adamantinoma of Mandible (aged 74 years), alive 12 months after 6×500 rads producing marked regression without recurrence of tumor

distant metastases already present in at least 8/22 (33 per cent) of cases.

- (b) Irradiations in HPO<sub>2</sub> consistently produced tumor regression in this group, generally acknowledged to be largely radioresistant, particularly in view of 73 per cent being recurrent after previous treatment. Marked regression was effected and maintained in 15/22 cases (68 per cent); autopsy examinations were performed revealing no evidence of residual disease in the irradiated zone in 8 cases. This overall response is an improvement on our previous experience with this type of case, and is clearly a testimony to the improved palliative value of a few HPO<sub>2</sub> treatments to afford more rapid and lasting results in relieving pain and in causing tumor regression.
- (c) Acute tissue reactions produced by  $3\times1,000$  rads over 3 weeks in HPO<sub>2</sub> appeared somewhat more severe than the same doses in air, but very similar to  $3\times2,700$  rads under conditions of tourniquet anoxia. So far, necrosis of normal joint cartilage and bone not invaded by tumor and covered by soft tissues has been observed infrequently with  $3\times1,000$  rads in HPO<sub>2</sub>.

### SOFT TISSUE SARCOMAS

The results are shown in Table XIII for 6 cases of locally recurrent disease and 3

cases of multiple lung metastases. Few conclusions can be drawn from this material which was hopeless from the outset. However, local regression of tumor masses was usually produced rapidly and maintained over the survival period. A massive recurrent fibrosarcoma of the thoracic sacrospinalis musculature responded dramatically to 3×1,000 rads in 3 weeks, but radiation pneumonitis was produced and caused death within 3 months, no residual tumor being detected at autopsy. A recurrent rhabdomyosarcoma of the thoracic spine in a 38 year old female, producing complete paraplegia, treated with 6×500 rads delivered at weekly intervals, has regressed, with a progressive recovery of sensation and muscular movements taking place over a period of 15 months, but the patient's pulmonary metastases are progressively increasing in size.

### TABLE XIII

SOFT TISSUE SARCOMAS TREATED BY HPO  $_2$  AND 4 MEV. ROENTGEN RAYS

9 cases

aged 17-75 years 1 Recurrence after Previous Surgery ± Roentgen-ray Therapy—6 cases Metastases demonstrated before treatment in  $HPO_{2}-2/6$ Survival at 12 Months—3/6 (4 dead at 3, 3, 5, 13 and 16 months; I alive at 15 months with metastases) Histology fibrosarcoma rhabdom yosarcoma I lymphosarcoma Regression Produced and Maintained-5/6 (clear at autopsy 2 cases) Causes of Death Metastasis 3 Cerebral hemorrhage Radiation pneumonitis

II Pulmonary Metastases Treated
Synovial sarcoma 2 (3×800 rads)
Fibrosarcoma I (2×1,000 rads)
Survival D<sub>4</sub> D<sub>10</sub> A<sub>6</sub>
Causes of Death
Radiation pneumonitis and liver damage 2
Recurrence I, alive at 6 months

Radical irradiation of large volumes of lung for pulmonary metastases in HPO<sub>2</sub> invariably produces radiation pneumonitis and death. It is interesting that at autopsy of 1 of these patients the upper portion of the right lobe of the liver, receiving  $2\times1,000$  rads in a week from being included in the fields, was necrotic.

### CONCLUSIONS

In this total series of 28 primary or locally recurrent sarcomas, lasting regression of tumor was produced by irradiation in HPO<sub>2</sub> in 20/28 cases (71 per cent). There was no evidence of residual tumor, based on autopsy findings, in at least 10 patients. The low survival rate of only 11/28 (40 per cent) cases surviving 12 months after treatment is no criterion of the efficacy of HPO2 in potentiating radiation effects. The greater predictability of producing rapid and lasting regression by irradiation given under conditions of hyperbaric oxygenation, in this group of so-called "radioresistant" neoplasms, testifies to the value of this modality. We have been unable to produce comparable consistent results in air, with either large fractions or daily fractionated high cumulative dose techniques, and the tissue reactions produced in HPO2 appear no more severe than with radical doses in air.

### DISCUSSION

Attempts to "equate" tumor and tissue pO2 by hyperbaric oxygen and tourniquet techniques, respectively, appear to improve the over-all results of radiotherapy in the treatment of bone and soft tissue sarcomas. This view is based on the more predictable tumor regression which has been obtained, particularly in larger tumors and those recurrent after previous surgery. Tissue reactions produced do not exceed those for similar radical treatments in air. However, survival of patients in this group is largely dependent on systemic factors, which local treatments such as surgery or radiotherapy do not significantly affect. The aim of local treatment is essentially to

produce lasting palliation and radiation must be delivered effectively and with radical intent if the patient is to benefit. In our experience, underdosage usually produces evanescent benefits and soon after the reactions subside and some comfort is achieved, local recurrence creates further discomfort and a demoralizing situation to both patient and therapist. Overdosage on the other hand causes distressing complications, which anoxic and hyperoxic techniques must also attempt to avoid.

It seems somewhat unreal for the radiotherapist to be overconcerned with the possibility of some late recurrence or inadequate local sterilization of tumors resulting in this group of disease, in which metastases almost invariably take their toll before such potential complications arise. It seems more real to aim at adequate regression and relief of symptoms for the duration of the patient's expected survival. One may well ask what the long term sequelae to radical irradiation of bone and soft tissue tumors are likely to be if eradication of the local primary condition were to be completely successful and the incidence of metastasis nil. Such radical irradiation, however administered, must invariably produce tissue atrophy and gross damage to cell replication processes and cloning potential—changes which are always subject to the incidence of radiation necrosis, particularly if injury should occur. Furthermore, high dosage irradiation delivered to benign conditions in bones is attended by a high risk of radiation induced neoplasia. This point is perhaps illustrated by our own survey of a series of cases of benign giant cell tumors, which received multiple courses of roentgen radiation. The survival curve is shown in Figure 2. A high incidence of deaths occurred 6 and more years after radiation treatments, most resulting from the development of radiation induced neoplasms in the irradiated area—tumors quite different in histopathology and malignancy from the benign condition originally

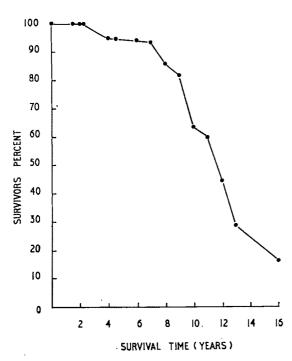


Fig. 2. Cumulative survival curve for patients receiving high dose orthovoltage radiation for benign giant cell tumor of bone (see text).

treated by roentgen radiation. One may well pose the question whether such changes would not occur equally in malignant disease of bone "cured" by radiation, if the patients were to survive their radiation treatments for an increasing number of years. A similar incidence of radiation induced neoplasms has been experienced in other benign conditions (see Table 1x, for example). We have recorded cases of such tumors arising after irradiation of benign conditions in children, with fractionated courses of as low as 2,000-3,000 rads, although most cases have been produced by long term, high dose, interrupted techniques, often doses as high as 12,000–20,000 rads having been prescribed for conditions in which the original clinicopathologic diagnosis was over-pessimistic or erroneous, a benign change being labelled as malignant or as one with "malignant potential."

It is concluded, therefore, that radiation techniques for malignant sarcomas should be primarily designed to produce optimum local control of the condition and to result in adequate and prolonged regression and useful function, consistent with a predicted survival. "Cure" is of secondary interest. If such cure seems likely after radical irradiation of limbs of younger patients, serious consideration must be given to electively amputate the limb before radiation effects produce potentially dangerous sequelae. It is considered that both tourniquet anoxia and hyperbaric oxygen techniques significantly improve the results of irradiation in a proportion of these tumors, provided the radiotherapist is not unduly concerned with chasing the myth of a "curative" result where such cure rarely exists. Our experience with these techniques indicates that adequate regression and palliation are usually produced which outlast the patient's survival—a result we have not experienced as frequently or consistently with more conventional methods of irradiation. The incidence of complications attributable to these techniques is low, and more than offset by a more predictable and rapid relief, expedited by a few treatments delivered over a relatively short period of time. Perhaps, if a high degree of selectivity is adopted in the choice of case material, small advantages in terms of prolonged survival may be demonstrable. However, this is of academic rather than practical clinical interest and excludes a majority of patients from beneficial therapeutics. Our experience does, however, indicate that ill-devised surgical procedures and socalled palliative radiotherapeutic regimens (based on underdosage) are pernicious practices which only interfere with subsequent attempts to provide palliation or cure.

### SUMMARY

1. Results are reported for cases of advanced and recurrent sarcomas of bone and soft tissues treated with 4 mev. roentgen rays under conditions of circulatory arrest produced by a tourniquet and in hyperbaric oxygen at 4 ATA, respectively.

- 2. The treatments have been administered to an initial series of 60 cases. Distant metastases were demonstrated in 19/60 (32 per cent) before treatment and a majority of cases treated were recurrent after surgery or roentgen-ray therapy.
- 3. The crude cumulative survival rate at 12 months differed for the two modalities, being 12/20 (60 per cent) in the tourniquet group and 7/22 (34 per cent) in the hyperbaric group, respectively. The difference is attributable to the stage of disease treated in the various groups.
- 4. Regression and sterilization rates of tumors produced were high with both anoxic and hyperbaric techniques, a pessimistic estimate of 70 per cent tumors resolving after the treatments which produced both acceptable levels of tissue reactions and tolerance. Absence of tumor was proven at autopsy or at amputations in 6 cases in the tourniquet group and in 10 cases in the hyperbaric group.
- 5. Dose fractionation regimens and calculations are described, and techniques and complications are discussed.
- 6. These results are compared with "conventional" radiotherapy results, and it is concluded that the "oxygen effect" provides the scope for improving over-all results of radiation therapy in this group of tumors.

H. A. S. van den Brenk, M.B.
Radiobiological and Hyperbaric Oxygen Research
Units
Cancer Institute Board
278 William Street
Melbourne, Australia

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Cloke. Miss D. O'Reilly is thanked for preparing the illustrations.

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# THE RADIOTHERAPEUTIC POSSIBILITIES OF NEGATIVE PIONS

### PRELIMINARY PHYSICAL EXPERIMENTS

By CHAIM RICHMAN,\* HENRY ACETO, Jr.,† MUNDUNDI R. RAJU,† and BERNARD SCHWARTZ†

BERKELEY, CALIFORNIA

BEAMS of roentgen rays have long been used in the treatment of cancer. Such beams were generally produced by 200 to 250 kilovolt machines. It was soon recognized, however, that roentgen rays of this energy leave much to be desired in treatment; for example, they give a high skin dose but have only limited penetrating qualities.

It was clear, therefore, that higherenergy quanta were desirable. Co<sup>60</sup> and Cs<sup>137</sup> sources and supervoltage machines have reduced the skin dose and increased the depth dose.

Cyclotrons and linear accelerators produce beams of particles with properties entirely different from those of roentgen rays and electrons, and great effort has been made to improve treatment techniques by use of these new radiations. The heavy charged particles produced by these high-energy machines—alpha particles, deuterons, and protons—undergo only small multiple-angle scattering, and can therefore be used where geometry is important. Also, such particles exhibit Bragg peaks at the ends of their ranges which can be useful in improving the ratio of dose in the tumor to dose in intervening tissue. 6,8,15 The Bragg peak is too narrow, however, to permit uniform irradiation of most tumors; furthermore, these charged particles do not have very high LET (linear energy transfer) except near the end of their travel. Variable absorbers may transform the Bragg peak into flat maxima of various lengths corresponding to the tumor dimensions, but this distribution of particles of different energies, with its associated spread

of energy over a larger volume, is achieved at the expense of the peak-to-plateau depth-dose advantage, and markedly decreases the average LET in the Bragg peak region.

When a beam of deuterons, for example, strikes a beryllium target, a useful beam of neutrons can be produced. The early work of Lawrence and co-workers suggested that neutrons, by virtue of their relatively high LET secondary protons, produce a greater biological effect on normal and neoplastic tissue than do roentgen rays.<sup>7</sup>

In 1938 a beam of high-energy neutrons was first used in the treatment of advanced cancer patients,14 but the results were not successful, owing to serious long-term damage to skin and to normal tissue, as reported by Stone.<sup>13</sup> More recently, Fowler et al.4 have revived interest with a series of pretherapeutic experiments with a neutron beam, designed to elucidate the long-term injury to normal tissues reported by Stone. The recoil protons, with energies of a few MeV, give rise to ionization densities of the order of 20 keV/ $\mu$ . For comparison, we note that 250 kV roentgen rays have LETs of about 3 keV/ $\mu$ , and gamma rays have LETs of less than 1 keV/ $\mu$ .

Pions are relatively new particles, discovered only about 20 years ago; there are positive, negative, and neutral pions. In this work we are concerned principally with negatively charged pions, or  $\pi^-$  mesons. The mass of the pion is between that of the electron and the proton; therefore, in passing through matter, the charged pion undergoes, in general, less Coulomb scattering than the electron and more than the

<sup>\*</sup> Graduate Research Center, Dallas, Texas.

<sup>†</sup> Donner Laboratory and Donner Pavilion, University of California, Berkeley, California.

proton, and in penetrating to a given range it produces less ionization per centimeter of tissue than the heavy proton. At the end of the pion range, new phenomena take place which have no counterpart with either electrons or protons. We are studying beams of pions to see if use of these unusual particles can improve on the present methods of irradiating tumors.

When negative pions come to rest in tissue, they are captured by the heavier elements-mainly carbon, oxygen, and nitrogen. This process produces an unstable nucleus, which explodes into shortrange heavily ionizing fragments, resulting in an augmented Bragg curve with an enhanced peak-to-plateau ratio. The capture events can be made to take place in the tumor region by so choosing the energy of the pions that they pass through the healthy tissue and stop in the tumor. Fowler and Perkins<sup>5</sup> were the first to make detailed calculations of the dosage to be expected from negative pions in tumors and in the surrounding tissue. Their results show that for negative pion beams the dose delivered in the tumor should be many times that in adjoining regions. Not only is the dose at the Bragg peak greater than the skin dose, but the increased ionization at the peak, with its concomitant increase in LET, produces a greater RBE (relative biological effect) as well.

The enhanced Bragg peak has another possible advantage in radiotherapy; there is a differential between the radiosensitivity of normal tissue and of a tumor when the oxygen supply to the tumor is impaired because of poor vascularization. That is, the anoxic or hypoxic cells are not killed so readily by roentgen rays and gamma rays as are well-oxygenated healthy cells. One way of overcoming this so-called oxygen effect is to use high LET radiation, which causes cell injury irrespective of the oxygen differential. With roentgen rays the biological effect produced is approximately 3 times as great under aerobic as under anaerobic conditions (i.e., oxygen enhancement factor ≈3). In contrast, this same ratio for the killing of mouse ascites tumor cells, as reported by Hornsey and Silini,<sup>4</sup> is 1.9 for neutrons of mean energy 6 MeV, whose average LET is approximately 20 keV/ $\mu$ . The highly ionizing alpha particles of mean energy around 6 MeV, resulting from nuclear absorption of pions in tissue nuclei, should be effective in further decreasing the differential oxygen effect.

The presently available negative pion beam is low in intensity; nevertheless, some dosimetric experiments can be done quite well; with care, it may even be possible in the future to do some biological studies of the RBE and the oxygen effect for pions.

In this paper we report measurements (by ionization chambers and LiF dosimeters) of the doses from the pion beam as a function of range in a Lucite phantom. We also studied the attenuation of the beam, by counting the particles with scintillators. In addition, we measured flux-density distribution in a plane perpendicular to the beam. Of fundamental importance is the energy release in the "stars" at the end of the range; we have investigated this with silicon semiconductor detectors. Finally, we have had to take a careful look (using a time-of-flight system) at the electron background in the beam.

### THE BEHAVIOR OF CHARGED PIONS IN TISSUE

Charged pions have a mass 276 times the electron mass; they weigh about  $\frac{1}{6}$  as much as protons. Unlike the electron and proton, the charged pion is unstable, and it decays in free space into a muon and a neutrino with a lifetime of  $\approx 2 \times 10^{-8}$  sec. This means that for any pion beam we produce, there will be a contamination of muons.

Charged pions traverse tissue like any particle of unit electronic charge. They stop after traveling a given range that depends on energy; e.g., a 50 MeV pion travels through about 10 cm. of tissue. In our work we usually use beams of energy around 90 MeV, which affords a good yield with a reasonable background.

STATE OF THE PARTY.

To make sure that the effects we are in-

terested in originated with the negativepion stars, we also studied positive-pion beams of the same energy. When the positive pion comes to rest in tissue, the Coulomb repulsion between the positive charges keeps it from interacting with the nuclei. It goes through two decay processes,

$$\pi^+ \rightarrow \mu^+ + \nu$$

followed by

$$\mu^+ \rightarrow e^+ + \nu + \bar{\nu}$$
.

The  $\nu$  and  $\bar{\nu}$  are neutrinos and do not contribute to dosage. The  $\mu^+$  is a short-range 4 MeV muon, which contributes a small dose. The positron in the second equation has a beta-spectrum energy distribution with a peak around 30 MeV, and a maximum of around 54 MeV.

The negative pion behaves differently from the positive pion: when a negative pion comes to rest, it is captured (because of its negative charge) by an atom in the tissue, and it cascades down the atomic levels of the atom in a time short compared with its lifetime. From the lowest atomic level it is captured by the nucleus, and the nucleus then explodes.

The type of breakup that one gets with the light nuclei has been studied by Ammiraju and Lederman, using a diffusion cloud chamber. They find that the release of energy in the ionizing fragments is particularly favorable in the light elements. For carbon the dominant reaction (25 per cent of the captures) turns out to be

$$\pi^- + C^{12} \rightarrow 2\alpha + 1p + 3n$$

where  $\alpha$  represents an alpha particle, p is a proton, and n a neutron. In nitrogen, the dominant reaction (19 per cent of the captures) is

$$\pi^- + N^{14} \rightarrow 3\alpha + 2n$$
.

The other reactions yield from 0 up to 5 charged particles, at times including a heavy ion. A few examples of this capture and resulting explosion as observed in nuclear emulsion<sup>10</sup> are shown in Figure 1. The alpha particles and protons have ranges of only a few mm. in tissue, and the neu-

trons produced here can be expected to contribute only a small dose to the tissue.

We see from these considerations that negative pions should have many advantages over roentgen rays, protons, or neutrons. They have an excellent depth dose to skin dose ratio. They traverse the healthy tissue with a low LET, and only in the tumor region does the LET become high. Here low energy alpha particles and protons are formed, and the average LET is about 20 keV/ $\mu$ . From experiments with other radiations, we know that the RBE increases with LET in this region, and that the absence of oxygen in a tumor has a smaller effect on the radiosensitivity of the tumor.

# THE PRODUCTION OF BEAMS OF NEGATIVE AND POSITIVE PIONS

Pions are secondary particles, and in our experiments they were produced by the Berkeley 184 inch synchrocyclotron. This machine provides an intense beam of 732 MeV protons that in their outer orbit strike a 2 inch beryllium target and produce neutral, positive, and negative pions. The experimental arrangement is shown in Figure 2. The negative pions are deflected out of the cyclotron by the cyclotron fringe field itself, and after leaving the cyclotron tank through a window, go through a small quadrupole focusing magnet, then along a channel through the main cyclotron shielding. Thereafter the pions enter a large shielded room called the meson cave, where various arrangements of magnets are used to bend and focus the pion beam. It is common to use a bending magnet followed by a quadrupole focusing magnet; frequently, however, we have used the bending magnet alone, which removes particles of different Hp from the pions that are being used. The cyclotron produces pions in a range of energies from o up to about 450 MeV; in our experiments, we used pions of 90 MeV, which have a range of 24 cm. of tissue.

The negative pions that come off in the direction of the proton beam are bent op-

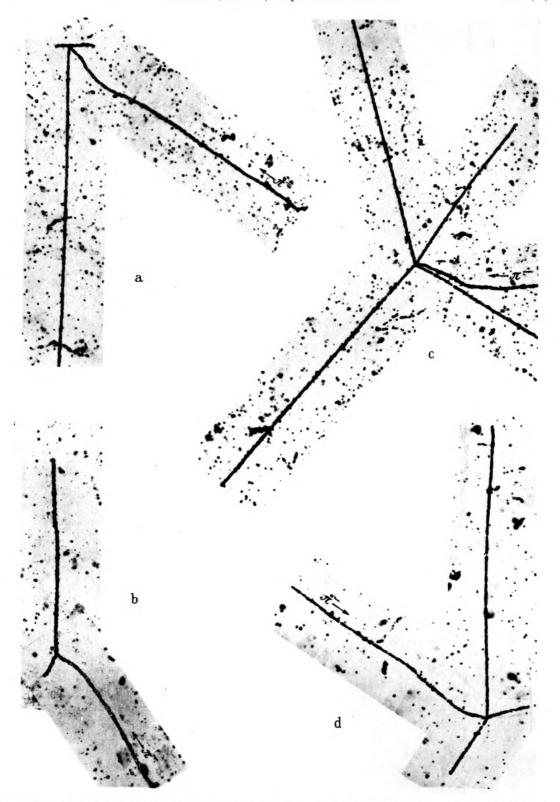


Fig. 1. Examples of the capture of negative pions and the resulting nuclear disintegrations in the light elements carbon, nitrogen, or oxygen as observed in nuclear emulsions. The pion tracks are labeled  $\pi^-$ ; the stars produced following their capture have various numbers of prongs.

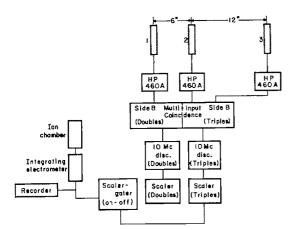


Fig. 4. Block diagram for the integral range experiment.

energies corresponding to the pion ranges at points A and B (94.5 and 108 MeV, respectively) of Figure 5. The spread in the pion energy is  $\pm 6.75$  MeV, which corresponds to a spread in momentum of  $\pm 8.4$ MeV/c. The muons in the final beam, resulting from the decay of pions before the beam reaches the analyzing magnet, have the same range of momentum as the pions. Because of their mass difference, pions and muons of the same momenta have different energies. In this case, the momenta correspond to a range of muon energies (point B to point C) which extends from 100 to 123 MeV, with an average energy of 116 MeV. These muons have a range about 30 per cent greater than the pions. If the muon contamination represents a sizable

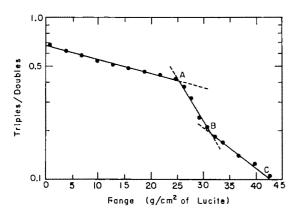


Fig. 5. The integral range curve for a negative pion beam of about 100 MeV.

fraction of the total beam, it may seriously affect the localization of energy. For this pion beam this contamination is approximately 10 per cent. The electron contamination can be estimated from the curve as 25 per cent of the beam. According to the integral-range data, the maximum intensity for this particular beam, after correction for the muon and electron contamination, is  $2 \times 10^4$  negative pions per cm.<sup>2</sup> per sec.

The time-of-flight experiment throws further light on these contaminations in the beam.

### MEASUREMENTS WITH IONIZATION CHAMBERS\*

The first dosimetric exposures to the beam were made with a Lucite phantom with sheets of roentgen-ray film placed between the slabs that made up the phantom. The film shows that the pion beam travels about 8 inches in Lucite, as expected. Beyond the range of the pions, there is a background of radiation visible on the film.

An ionization chamber 7 inches in diameter was used to maximize and monitor the beam; it was filled with a mixture of 96 per cent argon and 4 per cent carbon dioxide, at a pressure of 2 psi over atmospheric pressure. The saturation voltage was 1,000 volts.

We studied the pion beams by using one chamber as a monitor followed by different thicknesses of Lucite absorber and the second chamber as a detector. These first chambers were 2 inches deep in the beam direction, and used copper windows 5 mils thick.

Measurements were made for beams of both negative and positive pions. The Bragg peak for negative pions should be greater than and of somewhat different shape from that for positive pions. The difference between the two peaks is essentially, although not strictly, a measure

<sup>\*</sup>An account of these results appeared in the "Semiannual Report, Biology and Medicine, Donner Laboratory and Donner Pavilion," Lawrence Radiation Laboratory Report UCRL-11387, Spring 1964.

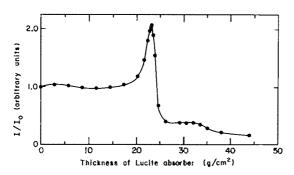


Fig. 6. The Bragg-type curve for a negative pion beam. The contaminations can be seen in the ionization beyond the main peak.

of the energy deposited in the chamber from capture events in the negative pion beam.

Figures 6 and 7 show the results of these experiments, where the measurements of the pion beam in the detector chamber (I) have both been normalized to the monitor chamber ( $I_0$ ). We note that with the positive pions there is very little background, but with the negative pions there is an appreciable background. This is understandable, since the positive pions are taken off backward from the proton beam to get them out of the cyclotron, while negative pions are taken off in the direction of the proton beam. The electrons and positrons are mainly forward.

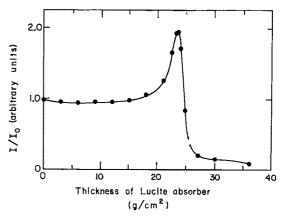


Fig. 7. The Bragg-type curve for a positive pion beam. In this beam the contaminations are quite low, as can be seen by the low ionization beyond the main peak.

To compare the two curves, we must subtract the backgrounds. The electrons undergo a great deal of multiple Coulomb scattering, and their contribution can vary at different thicknesses of absorber. As a first order approximation, we have taken the broad muon and electron plateau regions of the curve persisting beyond the Bragg peak to be the background at all points in the absorber. This gives a 40 per cent background to be subtracted for the negative pion beam. The resulting curves, normalized to unity for zero absorber thickness, are shown in Figure 8.

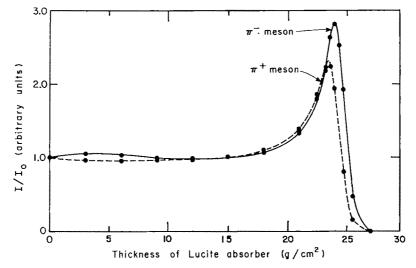


Fig. 8. A comparison of the Bragg-type curves for negative and positive pions, with the contaminations subtracted to a first approximation.

There is a difference in both shape and height of the two curves; the Bragg peak intensity for negative pions is 20 per cent above that for positive pions. Furthermore, the negative pion peak has been shifted to the right of the typical Bragg peak, as represented by positive pions. The new position of the peak corresponds roughly to the range of 90 MeV pions. This region also represents the place where most of the pions are stopping, and should show the contribution from the pion capture.

The interpretation of these curves is not as simple as one would like: first of all there is the uncertainty introduced by the background; then there is the fact that the nuclear fragments that are produced have ranges in our chamber which are much larger than the size of the chamber. This means that wall effects can be important. To study these effects, we built a 15 atmosphere chamber and filled it with nitrogen to simulate more closely the light nuclei in tissue. Within the accuracy of our experiments, we found no difference between the results with this chamber and the first chambers.

The peak dose is not so much larger than the entrance dose for negative pions as one might expect; however, more work needs to be done with improved beams.

The average dose found in one of our

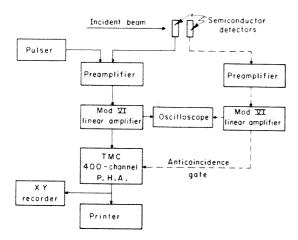


Fig. 9. Block diagram of electronics for the pulseheight analysis of a pion beam with semiconductor detectors.

beams was about 5 rad/hour, including the contaminations. This dose was also measured with LiF dosimeters and found to be about 5 rad/hour, with a peak-to-plateau ratio, again, of around 3:1. The dose distribution observed with these dosimeters confirms in a rough way the shape of the peak as observed with the ionization chambers; it must be added, however, that the LiF dosimeters have a basic limitation in the Bragg region, for they show a reduction in sensitivity of as much as 40 per cent for high LET radiations, so that the peak-to-plateau dose is probably higher than is indicated by these dosimeters.

# SEMICONDUCTOR DETECTORS

Semiconductor detectors are widely used because of their many advantageous properties. One of the most attractive features of these detectors is that the output is linearly proportional to the energy deposited.<sup>13</sup>

It is very important to know the energy distribution of the pion stars and to have a better measurement of the ratio of dose delivered at the end of the range to that at the entrance. Some measurements of the energy of the star fragments have been made with the diffusion cloud chamber<sup>1</sup> and emulsions.<sup>9</sup> In this study we have extended these measurements to include two different types of semiconductor detectors—a silicon surface-barrier-type detector and a lithium-drifted detector.

The experimental setup for both semiconductor detectors is shown in Figure 9. The test pulse generator used in the system was calibrated by using an Am<sup>241</sup> source, a Bi<sup>207</sup> internal conversion electron source, and particles from the heavy ion accelerator. The surface-barrier detector was calibrated by using the Am<sup>241</sup> source only, while the lithium-drifted detector calibration involved both sources. Lithiumdrifted detector experiments with alpha particles from the 184 inch cyclotron confirm the linearity of the system up to 85 MeV. The depletion layer of the surfacebarrier detector was chosen to correspond

to the range of the nuclear fragment of greatest importance to us—the alpha particle. The depletion layer thickness was 4.54×10<sup>-2</sup> g/cm.<sup>2</sup>, sufficient to absorb most of the alpha particle fragments. This thickness of silicon corresponds roughly to the ranges of a 20 MeV alpha particle, a 5 MeV proton, and a 0.22 MeV electron. Hence, a sizable portion of the nuclear energy released via protons escapes from the detector. Likewise, the contribution to the detector response by the incident pions, muons, and electrons is small. For any thickness of Lucite absorber, the total energy deposited in the depletion layer of the detector is given by the integral over all the channels of the products of the energy of the channel and the total counts in that channel.

The relative value of the energy absorption at the peak compared with that at the entrance (*i.e.*, tumor-skin ratio) is approximately 17:1, nearly 6 times the tumor-skin ratio measured with the ion chamber. Since the detector response has been maximized for response to the alpha fragments, this sizeable increase in energy deposition is due mainly to the alpha particles from the star events. In the light of the detector limitations, this ratio has little value as an absolute number; it sets an upper limit to the tumor-skin ratio.

The depletion region can be increased considerably by using a lithium-drifted silicon detector. Figure 10 shows the response of the unattenuated 180 MeV/c negative pion beam with its muon and electron contaminations of the same momenta. Two peaks, one at 0.87 MeV and the other at 1.05 MeV, are clearly visible. They are due to electrons and pions, respectively. The muon contamination, being small, is perhaps hidden in the distribution of the electrons and pions.

The width of the Bragg peak at the 50 per cent level as determined by the ionization chambers is approximately 1.8 g/cm.<sup>2</sup> of Lucite. The thickness of the semiconductor is 0.61 g/cm.<sup>2</sup>. Hence, if the detector is sitting at the Bragg peak position, a good

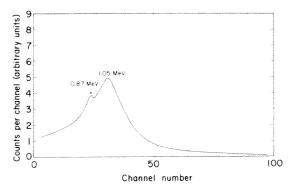


Fig. 10. The unattenuated negative pion beam as seen by lithium-drifted silicon detectors. The electron peak is at 0.87 MeV and the pion peak is at 1.05 MeV.

portion of the pions is stopped in the detector and creates stars in silicon. In order to see the energy distribution of the pion stars alone, the energy deposited by the pions, muons, and electrons through the detector has to be eliminated. When we add another semiconductor detector in anticoincidence with the analyzing detector, we observe only the pions that stop in the analyzing detector (i.e., pion stars), and the rest of the events can be eliminated. However, sometimes, one of the prongs of the stars in the first detector can pass through the second detector and cause an anticoincidence, thereby losing some stars. This does not affect the energy distribution of the pion stars appreciably. Figure 11 shows the energy distribution of the pion stars. The upper curve is the distribution obtained without using the second detector in anticoincidence. The bottom curve is obtained by using the anticoincidence detector, thereby giving the energy distribution of pion stars in silicon. Since the thickness of the detector corresponds to the range of approximately 84 MeV alpha particles and 20 MeV protons, this energy distribution of pion stars is not the total energy of the star but only that fraction of the energy of the star fragments deposited in the detector. Most of the alpha particles are stopped in the detector. Indeed, this is also true for the protons, except that some of the higher energy protons may de-

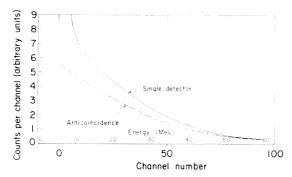


Fig. 11. The energy distribution of the negative pion endings in silicon, which is very nearly the energy distribution of the pion stars. The curve without the anticoincidence detector includes the pulses of particles passing through but not stopping in the analyzing detector.

posit only a small amount of their energy. On the other hand, neutrons escape the detector most of the time. It can be seen from the figure that the number of stars is a constantly decreasing function with energy, and that this star energy extends beyond 60 MeV. Since both curves are taken for the same amount of charge collected in the monitor, strictly speaking, they should coincide down to low energies. However, the lower curve (for anticoincidence detection) is less than the upper curve (for single detector), thereby indicating that some of the star events are lost when the anticoincidence detector is used because some of the fragments pass through the analyzing detector and reach the anticoincidence detector.

A calculation similar to that for the surface-barrier detector gives the energy deposited in the detector.

This method applied to the curves of Figures 10 and 11 gives the energy deposited in the detector on the plateau and in the Bragg peak region; the ratio of the two, for the same total flux of incident particles, is the tumor-skin ratio. The energy deposited in the silicon detector at the Bragg peak position, by this method, is about 5 times that at the entrance (i.e., tumor-skin dose ratio equals 5). It should be mentioned that this ratio was obtained by collimating the pion beam with a 2

square inch lead collimator upstream from the steering magnet. Later measurements with an uncollimated pion beam revealed a tumor-skin ratio of about 3:1, and even less. The amount of collimation used upstream from the steering magnet is important, since for equal settings of the steering magnet, this collimation determines the momentum spread of the beam. It can be seen that the tumor-skin dose ratio is a very sensitive inverse function of the momentum spread.

#### TIME OF FLIGHT

Our concern with the background radiation in the pion beam led us to a different approach. This method measures the time taken by each particle in the beam to traverse an extended path (which, in the setup in the pion cave, was approximately 23 feet). This system, developed by Nunamaker and co-workers, uses a  $4'' \times 4'' \times 1''$ plastic scintillator at each end of the flight path. The geometry of this experiment is therefore different from the other experiments. The velocity spectrum of the particles, as expressed by the time delay between the two detector responses, is fed to a time-to-pulse height converter and then to a PHA. The results were photographed on the cathode-ray tube.

Figure 12 shows four Polaroid pictures of the PHA display for a negative pion beam after passing through  $2\frac{1}{8}$ ,  $6\frac{1}{8}$ ,  $8\frac{5}{8}$ , and  $13\frac{1}{8}$ inches of Lucite absorber. For  $2\frac{1}{8}$  and  $6\frac{1}{8}$ inches of absorber, the beam is clearly differentiated into three distinct peaks representing the pions, muons, and electrons. Summation of a single peak gives the total number of particles represented by that peak. This procedure was repeated at several different depths in Lucite. One finds that the variation of the electron component with distance is similar to the exponential function obtained by using the integral range method. That is, both systems reveal a loss of about 25 per cent of the electrons in traversing a distance equal to the range of the pions in Lucite. This is shown in Figure 13. The percentage

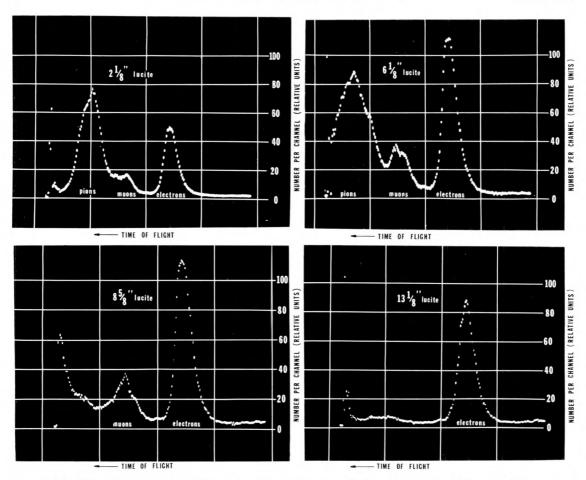


Fig. 12. The time of flight of the different particles in the negative pion beam after different thicknesses of Lucite absorber:  $2\frac{1}{8}$ ,  $6\frac{1}{8}$ ,  $8\frac{5}{8}$ , and  $13\frac{1}{8}$  inches. The scale setting on the PHA was 10<sup>4</sup> counts full scale for the run with  $2\frac{1}{8}$  inches of Lucite, but  $3\times10^3$  counts full scale for the others.

of electrons in the total beam of momentum 180 MeV/c increases linearly from 23 per cent at the surface to 40 per cent at the Bragg peak position in Lucite. These

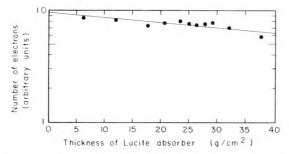


Fig. 13. The number of electrons as a function of distance in the absorber, calculated from the time-of-flight data.

results agree well with the integral range data.

#### CONCLUSIONS

This study of the physical properties of a negative pion beam shows that we can learn a great deal about these beams with the presently available intensities.

The different detection techniques and the different experiments have thrown light on the properties of such a beam. We have seen that the Bragg peak for a negative pion beam, as measured with a I atmosphere argon-carbon dioxide chamber, gives a peak-to-plateau ratio of around 3:1. This ratio is not so high as we expected; however, the ionization chamber is not the appropriate detector for the stars, be-

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cause the ranges of the nuclear fragments are frequently longer than the depth of the chamber. The semiconductor detectors are more appropriate for these phenomena; they give, in general, higher peak-to-plateau ratios.

The energy distribution of the stars has been determined very clearly for silicon.

We have utilized 90 to 100 MeV beams; a better beam for our work would be a 50 MeV beam, having a range of 10 cm. of tissue; this would obviate the large amount of slowing down of the particles with concomitant attenuation and scattering.

The large background of electrons and smaller background of muons obscure the nature of a beam. We hope to add an electrostatic separator in our experimental setup to remove these radiations.

Taken all together, a lower energy pion beam free of contaminations would make it possible, with the techniques that we have used, to look more carefully at the characteristics of negative pion beams.

Finally, we hope in the future to study the biological effects of pions, especially on the response of oxygenated and anoxic cells to the pion stars.

Chaim Richman
Lawrence Radiation Laboratory
University of California
Berkeley, California
and
Graduate Research Center
P.O. Box 30365
Dallas, Texas

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# RADIATION INDUCED CONDUCTIVITY AND THE STEM EFFECT\*

By L. B. BEENTJES, Ph.D., and F. A. GARRETT, M.A. GALVESTON, TEXAS

Two methods have been made an indica-WO methods have been advanced to chambers. One, actually giving an indication of the magnitude of this effect, uses an elongated field just wide enough to include the ionization chamber without its stem, in any penumbra, and about twice as long as the chamber. The output is first measured with the chamber axis along the field, and then with the chamber axis at right angles to the long axis of the field. Any difference in the two readings will be due to the stem effect.<sup>1,4</sup> A second method measures the effect by placing the ionization chamber, shielded by lead, outside the field exposing only stem and cap.4

Since the effect under consideration is relatively small and superimposed on the large chamber sensitivity to which it is merely additive and from which it does not differ selectively, the last method appears preferable. A restriction has to be made, namely, that the longer exposure times needed would not alter the stem behavior; otherwise, the two methods may yield different results. If, for example, the build-up of radiation induced conductivity until equilibrium would require hours, the stem effect would change with the number and duration of the measurements made, unless equilibrium would have been introduced by pre-exposure. Without the condition of pre-established equilibrium, repeated measurements could differ considerably, especially in the first method. Fowler and Farmer<sup>3</sup> indicate that the build up of the radiation induced conductivity is much more rapid than the recovery after the radiation has ended. Moreover, it is most rapid at high dose rates.

A summary of measurements of radiation induced conductivity in insulators has been recorded by Wintle.<sup>7</sup> He found that the conductivity of the insulator is well represented by the following expression:  $\sigma = kr^f$ , where  $\sigma$  is the conductivity, k a constant, r the exposure rate at the site of the insulator and f a constant between .5-I (see also Reference 2).

For insulators with f=1, equilibrium is reached in a few seconds; for insulators with f=.5, equilibrium is reached in a few hours. The Victoreen 25 r chamber utilizes polystyrene as insulating material. Fowler and Farmer<sup>3</sup> assigned to polystyrene an f value of .75; Wintle<sup>7</sup> takes a value of 1 over a wide range of r. Recovery takes in the order of  $5\infty$  hours.

From the formula  $\sigma = kr^{j}$  we draw the conclusion that the charge loss through the stem due to radiation will be given by

$$\Delta \mathcal{D} \text{ stem} = \int_0^{\tau} V(t) k_2 r^j dt$$

$$= \int_0^{\tau} \left( V_o + \frac{V_o - V_o}{\tau} t \right) k_2 r^j dt$$

$$= k_2 r^j \tau \frac{V_o + V_o}{2} = k_2 D r^{j-1} \frac{V_o + V_o}{2}$$

in which V is the voltage over the insulator,  $k_2$  a constant, t the exposure time,  $V_o$  the voltage at the onset of the radiation,  $V_o$  the voltage at the end of the radiation and D the exposure. On the other hand, the charge loss in the thimble will be given by

$$\Delta \mathcal{Q} \text{ thimble} = \int_0^{\tau} i dt = k_3 \int_0^{\tau} r dt = k_3 D,$$

where i = current and  $k_3$  is a constant.

<sup>\*</sup> From the Department of Radiology, University of Texas Medical Branch, Galveston, Texas.

Hence, the stem effect

$$\frac{\Delta \mathcal{Q} \text{ stem}}{\Delta \mathcal{Q} \text{ thimble}} = k_4 \frac{V_o + V_o}{2} r^{f-1}. \quad (1)^4$$

Thus it would appear that the stem effect would be linearly voltage dependent. In order to confirm the above expression, we have undertaken to measure the relative sensitivity of the stem as dependent upon the applied voltage.

# MATERIALS AND METHOD

The source used to provide the radiation was a Picker unit CBM-80 loaded with 6 kilocurie of cobalt 60. Measurements were made at 80 cm. distance from the source. The measuring device employed was a 25 r chamber, model 70-5 together with the Victoreen charger reader, model 570. Ten and one-half centimeters of the stem were exposed, the remainder of the chamber,

\* Without constants k2, k2, and k4:

$$\Delta \mathcal{Z} \text{ stem} = \frac{1}{R} \left( \frac{V_{\bullet} + V_{c}}{2} \right) \tau_{i}$$

where R = stem resistance.  $R = a/A\sigma$ , in which a = depth of conductor; A = area.

$$R = \int_{a_1}^{a_2} \frac{da}{2\pi a l \sigma} = \frac{1}{2\pi l \sigma} \int_{a_1}^{a_2} \frac{da}{a} = \frac{\ln a_2/a_1}{2\pi l \sigma},$$

in which I is the stem length;  $a_1$ =.075 cm. (central electrode);  $a_2$ =.625 cm. (outer electrode).

$$\Delta \mathcal{Q} \text{ stem} = \frac{2\pi l\sigma}{\ln \sigma_2/\sigma_1} \frac{V_o + V_o}{2} r = \frac{\pi lkr^f(V_o + V_o)\tau}{\ln \sigma_2/\sigma_1}$$

$$\Delta 2 \text{ thimble} = \frac{1}{60} r \times \frac{1}{3} \times 10^{-19} \times v \times \tau,$$

in which  $r = \exp o s$  are rate in roentgens/min.; v = thimble volume in cc.; 1.83 for the 25 r chamber.

Stem effect = 
$$\frac{\pi l k r^{d-1} (V_o + V_o) \times 18 \times 10^{12}}{v \ln a_2/a_1}$$

Using Wintle's values, this would yield an expected stem effect (10.5 cm. stem) of .14 per cent; using Fowler and Farmer's values .009 per cent. The measured value was

including the thimble, being shielded by 20 cm. of lead. Exposure was made for various lengths of time ranging from 3 minutes to 28 minutes. These exposures would yield different final voltages, thus providing various  $V_{\bullet}$ . We also used a radiation field 2.4 cm. wide and 6 cm. high to investigate if the stem contribution would be linear with the exposed stem length.<sup>5,6</sup> The chamber was moved 1 cm. at a time through this field, using appropriate exposure times to give readings accurate within 5 per cent.

#### RESULTS

We have expressed the current induced in the stem as r per minute. Figure 1 shows this current plotted against that percentage of the full scale at which the reading was obtained. The exposure rate at the site of the stem was 140 r per minute. The graph shows that, instead of a 100 per cent reading at full scale, only 74 per cent occurs. The linearity of the instrument was better than 1 per cent through 80 per cent of the full scale. Since our  $V_0 = 533$  and  $V_0 = 222$  ( $V_0$  charger = 280 V), a calculated value of 71 per cent would be expected according to formula (1). This is in full agreement with the measurements being within the limit of error.

# CONCLUSION

The stem effect is not merely dependent upon the exposed stem length but also upon the voltage between the electrodes. When the stem effect is known at a certain position on the reading scale, a graph can be made if beginning voltage and full scale voltage of the ionization chamber are known. One simply takes into account the linear drop-off of the stem effect with the voltage, similar as in Graph I. The National Bureau of Standards provides the pertinent voltage data with its routine calibration service. The chamber voltage can be calculated from this.

One should make certain that equilibrium has been established in the insulator

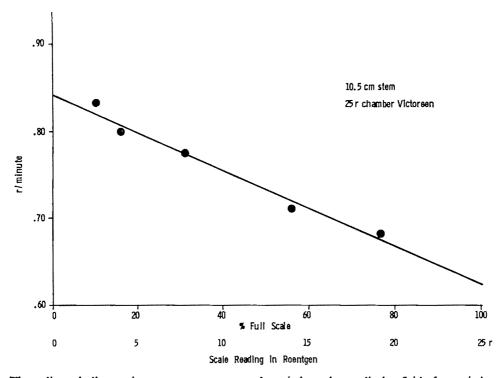


Fig. 1. The ordinate indicates the stem current expressed as r/minute in a radiation field of 140 r/minute. The abscissa indicates the percentage of the full scale on the electrometer. This percentage is linearly related to the voltage on the chamber before reading. At V = 533, the r/minute value is .84, and at V = 280, the value is .62.

before the stem effect is measured. From Formula (1) it follows that a dependence on the exposure rate is to be expected as well if  $k \neq 1$ . Generally, the stem effect should be small, but in measurements with electrons it may amount to more than 10 per cent.<sup>6</sup> Of course, better calibrating instruments should be used in this case whenever available.

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# SUMMARY

It is shown that the stem effect is not a constant fraction but a variable, changing with the voltage between the electrodes. The linearity of the stem effect has been checked also as a function of exposed stem length by measurement of the contributions of parts of the pure stem.

L. B. Beentjes, Ph.D. The University of Texas—Medical Branch Galveston, Texas

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# SIGNIFICANCE OF R, RAD, REM, AND RELATED UNITS\*

By MARVIN M. D. WILLIAMS, Ph.D. ROCHESTER, MINNESOTA

SOME of the definitions and terms used to describe quantity, quality, and dose of roentgen rays have been changed several times since some of them were first adopted in 1928. Also some new terms and units have been added. The original definitions and units were quite satisfactory in 1928 for the radiations available and the knowledge of their interactions with matter. Both the clarification of older definitions and the addition of some new terms have become necessary because (1) more is known about the interactions of radiations with matter and the biologic effects of radiation, (2) there have been new developments in radiation detecting and measuring equipment, (3) higher energy roentgen rays and new corpuscular radiations have become available, and (4) the increase in international communications requires the use of terms having similar meanings in many languages. These terms must be used correctly if radiologists are to communicate with each other, and these terms can be used correctly only if they are understood.

The definitions of units and quantities adopted in 1962 by the International Commission on Radiological Units and Measurements (ICRU) are the result of several years of intensive study by subcommittees appointed for this purpose. It is unlikely that the definitions will be changed significantly in the near future. A thorough discussion of these definitions, a few of which will be discussed here, can be found in a series of National Bureau of Standards Handbooks.<sup>2-4</sup>

Before proceeding with a discussion of the terms, it may be worthwhile to review some basic physics. Radiation, which is energy in motion, produces an effect only if energy is transferred to matter. The only effect radiation can produce in matter is to increase its energy content. The process of transferring energy from radiation to matter takes place in two steps: the radiation (photons) transfers energy to electrons (secondary electrons) which then distribute the energy to the matter. The energy delivered to a single electron depends on the energy of the photon and the kind of interaction it had with the electron (photoelectric, Compton). The length of the path along which the secondary electron distributes the energy which was given to it depends on the energy of the electron and the physical characteristics, primarily density, of the matter. Depending on its energy, an electron will travel up to several meters in air and several millimeters in soft tissue (Table 1). When photons are capable of producing high-energy secondary electrons, it is possible that the amount of energy transferred from photons to electrons within a volume may be very different from the energy actually delivered to that volume; secondary electrons originating in a volumemay lose most of their energy in surrounding volumes, while most of the energy actually delivered to a volume may be received from electrons originating in the surrounding volumes.

When radiation is used as a diagnostic tool, the radiologist wishes to produce as little biologic effect as possible; when the radiation is used as a therapeutic agent, the primary aim is to produce a biologic effect. In either instance, then, he is interested in the amount of energy delivered to (absorbed by) a mass of tissue. It is to

From the Mayo Clinic and Mayo Foundation: Section of Biophysics.

<sup>\*</sup> Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28 to October 1, 1965.

TABLE I
RANGE OF ELECTRONS

Electron energy (MeV.)	Range		
	In air (cm.)	In water (mm.)	
0.01	0.225	0.0021	
0.02	0.77	0.0076	
0.03	1.60	0.016	
0.05	3.85	0.039	
0.1	12.4	0.13	
0.2	39.0	0.42	
0.3	73.5	0.78	
0.5	162.0	1.7	
1.0	395.0	4.6	
2.0	890.0	10.0	
3.0	1300.0	15.0	
5.0	2250.0	26.0	

this absorbed energy that the term "dose" refers. The unit of dose is the rad; a dose of I rad has been delivered when the energy absorbed amounts to  $1\infty$  ergs per gram of irradiated matter.

The measurement of the amount of energy absorbed in a mass has been difficult to make, and such measurements have seldom been made in the past. Some of the new measuring equipment may allow measurements of absorbed energy to be made easily.

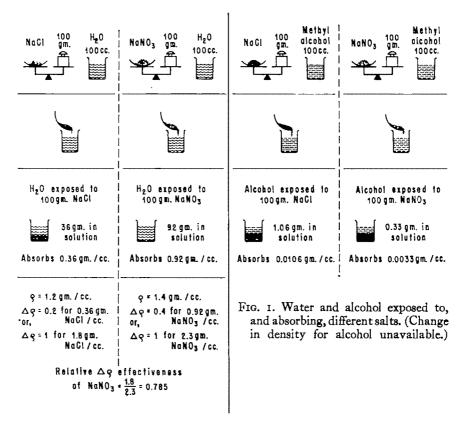
The common method used to measure roentgen rays is to measure the amount of ionization produced in a small volume of air. The common unit for measuring ionization in air is the roentgen, designated by "R," which is the unit of exposure. An exposure of I R has been given when, under certain specified conditions, the number of negative or positive ions produced in 0.001293 gm. of air amounts to I electrostatic unit of charge.

However, the definition of the roentgen makes no reference to the amount of ionization produced in 0.001293 gm. of air. What the definition does say is that the secondary electrons—corpuscular emission—originating in 0.001293 gm. of air shall produce in air I electrostatic unit of charge of either sign. Because the range of the sec-

ondary electrons in air is generally many centimeters, the ionization produced in any small mass of air is mostly produced by secondary electrons which originated in surrounding volumes. It is not possible to measure what is specified by the definition, but it is possible to measure an amount of ionization equivalent to that specified by the definition if electronic equilibrium exists in a small volume of air. Electronic equilibrium means that the amount of ionization produced in a volume of air by secondary electrons which have originated outside of that volume is just equal to the ionization produced outside of that volume by secondary electrons which have originated inside the volume. The "certain specified conditions" (mentioned in the previous paragraph) are those conditions which produce electronic equilibrium. They relate to such factors as the material and thickness of the wall of the ionization chamber. Occasionally, electronic equilibrium may exist in a volume of irradiated air at the point at which a measurement is to be made, but commonly the ionization chamber itself produces a condition of electronic equilibrium which otherwise would

The roentgen gives no information about the number of photons available, the energy of the photons, the fraction of the available energy which was transferred to electrons, or the amount of energy which would be delivered to a volume of air at that position if the ionization chamber were not present. The exposure at a point, specified in roentgens, is a property of a beam of photons expressing its capability to deliver energy to electrons in a small volume of air if a small volume of air were placed at that point.

The fraction of the available energy which will be delivered to a volume of matter depends on the energy of the photons, the environment of the volume, and the chemical composition of the matter occupying that volume. So the ratio of exposure (R) to the energy which will be absorbed by the matter (rads), placed at the



point where the exposure was measured, will depend on the quality of the radiation, whether electronic equilibrium exists in the matter, and the kind of matter.

To understand the difference between exposure, measured in roentgens, and dose, measured in rads, is essential for the proper understanding of radiation reactions. Exposure measures one property of the beam of radiation—its ability to produce corpuscles in a volume of air—and has proven to be useful for comparing beams of radiation of similar quality. Dose measures the energy actually delivered to the irradiated material and is that which is responsible for producing radiation effects.

One of many possible analogies which may illustrate some of the principles being discussed is the problem of changing the density of liquids by dissolving salts in them (Fig. 1). If one pours 100 gm. of NaCl into a beaker containing 100 cc. of water and 100 gm. of NaNO<sub>2</sub> into another such beaker, it will be found that 36 gm. of

NaCl and 92 gm. of NaNO<sub>8</sub> will dissolve in the water. If these salts had been poured into alcohol instead of water, 1.06 gm. of NaCl and 0.33 gm. of NaNO<sub>3</sub> would have dissolved in the alcohol.

Although it is common to refer to  $1\infty$  gm. of two salts as being the same amount of each salt, they are not the same in volume, number of atoms, or number of molecules; they are the same only in their ability to affect a balance. Similarly  $1\infty$  R of two roentgen-ray beams of different half-value layers (HVL) do not contain the same amount of energy or the same number of photons; they are the same only in their ability to affect a roentgen meter—their ability to produce secondary electrons in a volume of air.

The 100 cc. of water do not dissolve the same amounts of the two slats to which they are exposed, and different liquids will not dissolve the same amounts of the two salts. Similarly, one kind of tissue may absorb different amounts of energy—receive

different doses—when exposed to the same number of roentgens of two qualities of roentgen rays; different kinds of tissue exposed to the same radiations may receive quite different doses. Just as the solubility factor depends on the salt and the liquid, so the conversion factor for calculating the rad dose from the R exposure depends on the quality of the radiation and the kind of tissue.

At the beginning of this analogy, the aim was stated to be to change the density of liquids by dissolving salts in them. If the densities of such solutions are determined, it can be calculated that the same weights of different salts in solution will produce different changes in density of the liquids. This might be expressed by saying that the relative density-changing effectiveness of a salt depends on the particular salt and liquid combination. Similarly, it is known that the same doses—rads—of radiations of different qualities delivered to similar tissues, or the same doses of radiations of the same quality delivered to different kinds of tissue, may not produce the same biologic effect. This concept can be expressed by saying that the relative biologic effectiveness (RBE) of a radiation depends on the quality or kind of radiation used and the kind of tissue irradiated. The RBE of a radiation is the ratio of the dose of a standard radiation required to produce a biologic effect to the dose of the radiation being investigated which is required to produce the same biologic effect, when both doses are given in a similar manner. The standard radiation generally is 200 kv. roentgen rays.

In addition to quality of radiation and kind of tissue, the RBE depends also on such factors as the dose distribution in the irradiated volume, the rate at which the radiation is delivered, the particular biologic effect being observed, and numerous other biologic factors. It is of most importance in the field of radiobiology. A specific RBE value can apply for only one set of factors, and few specific values are known at present. Even though RBE values cannot be applied to many practical situations, it is

very important for a radiologist to know that equal doses of all radiations may not produce the same biologic effect in all tissues.

One physical factor which causes a variation in RBE is the rate at which energy is lost along the path of an electron or other ionizing particle; this is referred to as the linear energy transfer (LET). The LET depends primarily on the velocity of, and the quantity of charge on, the ionizing particle. That part of the RBE which depends on the LET is now called the quality factor (QF) and has values from 1 to as high as 15 or 20. Values of QF vary somewhat for different tissues and for different biologic effects. Exact values of QF are not known, but approximate values and the approximate ranges of values for different kinds of radiation are known. The product of rads by QF (and at times by other modifying factors, such as that due to unequal dose distribution) gives a quantity which should be nearly proportional to the biologic effect; this quantity is called the dose equivalent, is measured in rems, and is used in the field of protection. The following example will illustrate its importance in this field. A dose to a radiation worker of 0.05 rad in a week from radiation with a QF of 1, a dose equivalent of 0.05 rem, would be a rather unimportant dose; but the same dose from radiation with a QF of 15, a dose equivalent of 0.75 rem, would be of some concern. The biologic effect produced by a dose of 0.05 rad from radiation with a QF of 15 would be comparable to that produced by a dose of 0.75 rad from radiation with a QF of 1; both doses would be dose equivalents of 0.75 rem.

In the field of protection it is not feasible to measure exposures or doses with great accuracy. Generally, the aim is to know the order of magnitude of biologic damage which may be produced. The use of QF values which are a maximum for the kind of radiation producing the dose is desirable, since it tends to provide some factor of safety. Because for most roentgen and gamma rays the conversion factor for cal-

culating rads from R does not differ greatly from I, and the QF factor also is about I, it is generally assumed for protection purposes that an exposure of I R delivers a dose of I rad and a dose equivalent of I rem when all of the exposure has been to the roentgenray and gamma-ray qualities commonly used in medical institutions. However, if some of the dose has been received from heavy particles for which the QF values are generally large, it is essential to know the QF values for those particles to properly evaluate the significance of the dose.

Roentgen-ray equipment operating at less than 3 million volts (Mv.) is customarily calibrated in terms of exposure measured in air with no scattering material in the beam; this is frequently referred to as the air exposure. The exposure to any irradiated tissue is commonly determined by using relative depth-dose tables\* and isodose charts which give the exposure, including that from both the primary radiation and the scattered radiation, of the tissue relative to the air exposure. The dose is

then calculated by multiplying the exposure by a conversion factor,  $\bar{f}$ , for the kind of tissue being irradiated and the quality of the radiation producing the exposure.<sup>3</sup>

This procedure for calculating dose is quite straightforward in principle. In practice, there are many sources of error and some of the necessary data often are not available. The air exposures used may be in error by 20 per cent or more; the depthdose tables and isodose charts used may introduce errors of 10 per cent or more; the inhomogeneity of the tissues, if it is not taken into account, may produce errors of 30 per cent or more; and the value of  $\overline{f}$ , if it is not for the quality of the radiation actually delivering the dose, may be in error by 50 per cent or more. All of these errors are not likely to be additive, and the maximum values are not likely to apply to a single situation; however, these and other similar errors are quite likely to result in an error of 40 per cent or more in the calculated dose.

The air exposure may be in error because of several reasons. The exposure generally varies with the size of the irradiated area determined by cones or other collimating devices (Fig. 2), and this frequently is not known or not taken into account. The ex-

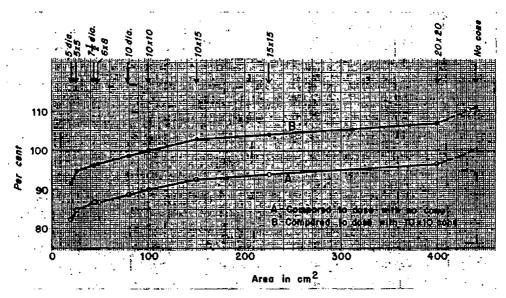


Fig. 2. Variation in exposure due to changes in field size as determined by cones. (Measured in air, 5 cm. below cone; 250 kv., 0.5 mm. Cu.)

<sup>\*</sup> These terms are used in this discussion because they are the commonly used terms. In some instances, including this discussion, more accurate terms would be relative depth-exposure tables and isoexposure charis.

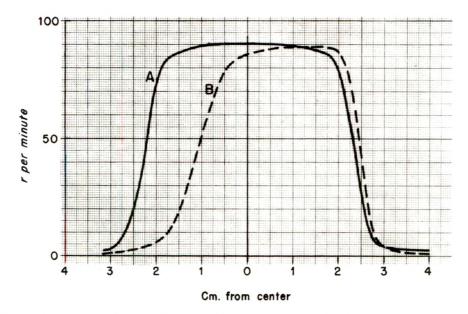


Fig. 3. Variation in exposure at bottom of cone, 5 by 5 cm., along line perpendicular to tube axis with cone in two positions (rotated 180°) in cone holder.

posure over the area may vary a great deal and may even be negligible over a considerable part of the area (Fig. 3). There may be considerable scattered radiation near the bottom of a cone which will affect the exposure near the surface but not at a depth of more than a few centimeters (Fig. 4). Other sources of error may be due to such factors as an incorrectly calibrated or an improperly used exposure meter.

The depth-dose tables and isodose charts may not be suitable for the equipment delivering the radiation. Various published depth-dose data differ considerably (Fig. 5); this may be due in part to differences in collimating devices or other variations in equipment.

The common depth-dose tables and isodose charts have been made from data obtained in a homogeneous medium, most commonly water or other unit-density material. The attenuation of radiation is different in fat, muscle, and bone. Failure to take this into account can cause large errors in the calculated exposure, particularly if the radiation passes through a considerable thickness of bone (Fig. 6).

The conversion factor by which the ex-

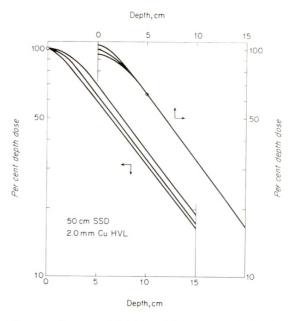


Fig. 4. Some published central axis percentage depth-dose data. At left, data are normalized at surface and show large differences at all depths except at surface. At right, same data are normalized at depth of 5 cm.; this shows good agreement at clinically important depths below 5 cm.; only at the clinically relatively unimportant regions near the surface are there appreciable differences, due largely to radiation scattered from sides and bottom of cones. (Modified from data in National Bureau of Standards Handbook 87.4)

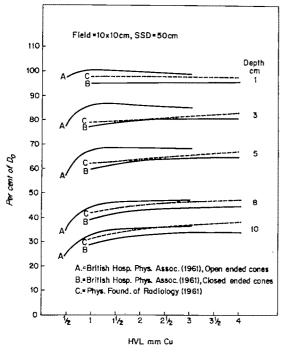


Fig. 5. Comparison of depth-dose data from two sources<sup>1.6</sup> for various qualities of radiation at several depths. If these data were normalized for depth of 5 cm. instead of for the surface, curves A and B would differ by less than 1 per cent for nearly all points except for those at 1 cm. depth; the percentage difference between curves C and B would be less that in this graph, but would still be appreciable.

posure is to be multiplied to obtain the dose, converting R to rads, varies with the kind of tissue and the quality of the radiation. Figure 7 shows this variation of  $\overline{f}$  for muscle and bone over the range of qualities included in orthovoltage therapy. The values for muscle change by less than 5 per cent with this variation in quality; but for bone the variation is more than fourfold. The value for fat is about half that for muscle for very soft qualities of radiation but rises quickly, as the HVL increases, to a value of about the same as for muscle. For harder qualities, such as cobalt 60 radiation and radiation generated at a few Mv., the conversion factor is lowest for bone and highest for fat; but values for the three tissues are not very different. If a value of about 0.945 is used for muscle, the error

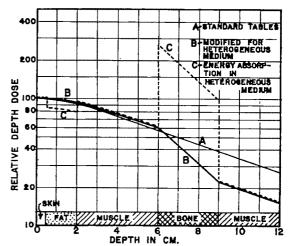


Fig. 6. Effect of tissue inhomogeneities on exposure and dose, for HVL of 1.5 mm. Cu, 50 cm. SSD, and field area of 100 sq. cm. (Reproduced with permission from Johns, H. E. The Physics of Radiation Therapy. Charles C Thomas, Publisher, Springfield, Illinois, 1953, 286 pp.<sup>5</sup>)

probably will be not more than 3 per cent regardless of the quality of the radiation; however, for bone, a value for the quality of the radiation delivering the dose must be used or an error of 100 per cent or more may occur.

The quality, HVL, of the radiation is customarily determined for the primary beam entering the tissue. In the orthovoltage range, Compton scattering is an im-

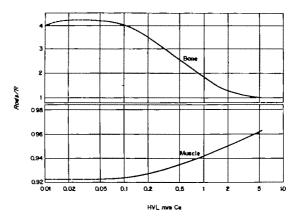


Fig. 7. Conversion factors,  $\vec{j}$ , for converting R to rads, for muscle and bone, for commonly used qualities of radiation. (Modified from data in National Bureau of Standards Handbook 85.3)

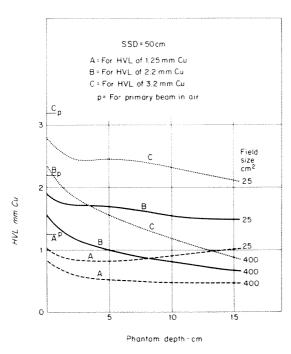


Fig. 8. HVL of radiation responsible for exposure at various depths within homogeneous phantom of unit-density material, for two field sizes of three different qualities of incident radiation. (Plotted from data in Skarsgard, L. D. and Johns, H. E.<sup>7</sup>)

portant interaction, and scattered radiation may account for as much as a third of the exposure at the surface and for as much as 90 per cent at a depth. The presence of this scattered radiation changes the quality of the radiation responsible for the exposure. Figure 8 shows that this change in quality may be very great and that the change depends on the quality of the primary beam, the size of the field, and the depth. These values are for a homogeneous medium of unit density; inhomogeneities, such as bone, in the path of radiation would alter the data. Data of this kind are available for only a very few combinations of HVL, source skin distance (SSD), and field size.

Values of  $\bar{f}$  for bone being irradiated with the HVLs shown in Figure 8 have been taken from Figure 7 and plotted in Figure 9. It is evident that, for calculating the dose delivered to bone, the use of a conversion factor for the HVL of the incident radiation, as is frequently done, is likely to give a value very different from the correct value, and the dose so calculated may have little significance.

It may be worth noting that the  $\bar{f}$  values for bone in Figure 7 are those for compact bone. Since many bone tumors consist of soft tissues, or a mixture of soft tissue in compact bone, the correct value of  $\bar{f}$  may be very difficult to determine.

Perhaps it would be better not to try to calculate the dose, unless it is done accurately, than to make an approximate calculation with a large probable error. The fact that one has gone through a procedure of calculating a new quantity—rads from R—is likely to produce a feeling that the new value is of greater significance. Actually, if the calculation gives an incorrect value, its significance may be less than that of the value from which it was calculated. It may be better in many instances not to attempt to calculate the dose but to record the exposure with sufficient information to per-

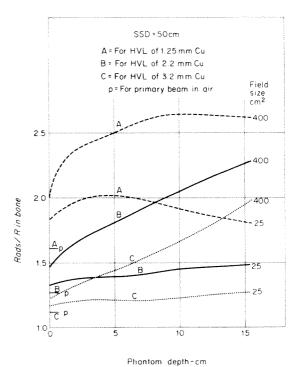


Fig. 9. The  $\bar{f}$  values for bone irradiated at various depths in phantom, for two field sizes of three different qualities of incident radiation. Data calculated from data shown in Figures 7 and 8.

mit reproduction of the exposure and, if desired, later evaluation in terms of dose.

Since exposure cannot be determined for radiation generated above about 3 Mv., it seems best to calibrate the equipment in terms of the dose that will be delivered to unit-density tissue at the depth of maximum dose. The dose reaching tissues at other points may then be expressed in values relative to this maximum, on the assumption that all of the irradiated tissues are of unit density. To determine the true dose, it will then be necessary to make corrections for the presence of tissues of other than unit density and for possible significant changes in the quality of the radiation. For these high energy radiations, as compared to radiations in the orthovoltage range, there is less difference in the attenuation of the beam as it passes through different tissues, there is less change of quality with depth, and there is less dependence of the values of  $\bar{f}$  on the quality of the radiation and the kind of

No attempt has been made to discuss all of the terminology of the physics of radiology with which a radiologist should be familiar or to discuss all of the problems related to Rs, rads, and rems. An effort has been made to show that there is an important difference between exposure, which is measured in roentgens, and dose, which is measured in rads. This difference is a very important and basic one which should be understood by all radiologists. Biologic response to irradiation may be expected to have some correlation with dose, but frequently may have no correlation with exposure. Although the method of calculating dose from exposure, particularly in the

orthovoltage range, is quite straightforward, it frequently is not possible to make an accurate calculation because accurate and sufficient information is not available. Inaccurate determinations of dose, either because of faulty or insufficient data or because of unavailable data, may result in values of dose which are of less significance than the values of the exposure from which they were calculated; and, in fact, such dose values may be misleading.

The Mayo Clinic Rochester, Minnesota 55902

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# THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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# M EDITORIALS M

# THE AMERICAN RADIUM SOCIETY AND THE JOURNAL

# FIFTY YEARS OF SCIENTIFIC ADVANCEMENT

CINCE the foundation of the American Radium Society, fifty years ago, tremendous advancements have been made in the scientific application of radium, and with it or subsequent to it, of other types of ionizing radiations for the treatment of disease. Truly reflecting this advancement, the Society grew in importance and scope. In observing the Golden Anniversary, it celebrates the Valhalla of its pioneer members, who in their unswerving devotion to science with indomitable idealism blazed the trail of a high endeavor, and also pays due tribute to the many members who participated in and contributed to the attainment of such a high endeavor. The JOURNAL over this half century gave faithful expression, through its pages, to the many successive phases of this astounding advancement, some of which may be of pertinent interest at the present Anniversary celebration.

The American Radium Society was founded in 1916.1 As the result of the work of a temporary organization, which held a conference during the American Medical Association Convention in Detroit, Michigan, in June, 1916, some 24 physicians interested in the subject of radium held a meeting at the Ritterhouse Hotel in Philadelphia, Pennsylvania, Thursday, October 26 at seven o'clock. It was unanimously decided that such a Society was greatly desired and those present immediately agreed to adopt a constitution and bylaws. It was defined in this constitution that, "The object of the Society is to promote the scientific study of radium in relation to its

<sup>1</sup> The American Radium Society. Editorial. Am. J. ROENT-GENGL., 1916, 3, 594. physical properties and its therapeutic application."

From the very beginning, most of the papers read at the subsequent Annual Meetings of the Society were published unofficially in the American Journal of Roentgenology, the official organ of the American Roentgen Ray Society. Consequently, a desire was expressed to adopt this Journal also as the official organ of the American Radium Society.

On April 26, 1920, at the Fifth Annual Meeting of the American Radium Society held in New Orleans, Louisiana, with Dr. Henry K. Pancoast presiding, the AMERICAN JOURNAL OF ROENTGENOLOGY was made the official organ of the Society.<sup>2</sup>

In September, 1922, at the Twenty-third Annual Meeting of the American Roentgen Ray Society, which was held at Los Angeles, California, the Executive Council unanimously voted to change the name of its official Journal so as to read The American Journal of Roentgenology & Radium Therapy. This step was thought advisable in view of the increased prominence of radium therapy and the fact that the American Radium Society had made this Journal its official organ.<sup>8</sup>

The January, 1923, issue carried the title of The American Journal of Roentgenology & Radium Therapy. Since then all submitted papers and other pertinent material of the American Radium Society were officially published in the Journal.

This resulted in a formidable accumula-

<sup>&</sup>lt;sup>2</sup> The American Radium Society. Fifth Annual Meeting, April 26, 1920, New Orleans, Louisians. Am. J. ROENTGENOL., 1920, 7, 362–363.

<sup>\*</sup> A change in the name of the Journal Editorial Am. J. ROENT-GENOL., 1922, 9, 688.

tion of contemporary scientific information on the advancement of knowledge. A very vivid, and at times quite personal, chronicle of the early history of radium therapy and the American Radium Society (up to 1934) was given by Case;<sup>4,5</sup> and the background of radium therapy in the United States (1906–1956), together with many salient events of the American Radium Society, was masterfully depicted by Quimby<sup>6</sup> on the occasion of the Fiftieth Anniversary of the Journal.

A perusal of this noteworthy literature reveals the inescapable fact that as the Society grew in scope and its Annual Meetings had to be programmed with more and more contributions, a central theme, highlighting the contemporary facet of the meeting, became desirable. The Society was already greatly indebted to Henry Harrington Janeway, Head of the Radium Department of the Memorial Hospital, New York, and an ardent member of the Society during the few years between its founding and his death in 1923.7 He, with Quick, Failla and Quimby, exerted notable efforts to standardize dosage and render the application of radium more accurate in the treatment of uterine carcinoma particularly, and was the first in America to use radium emanation buried in tumor growths. It was fitting, therefore, that a Lecture should be established honoring his immortal attributes. In 1932, at the Annual Meeting of the Radiological Society of North America in Atlantic City, New Jersey, Dr. Burton J. Lee, the President of the American Radium Society for 1933, with other members of the Society, laid the groundwork for the found-

<sup>4</sup> Case, J. T. Some early experiences in therapeutic radiology; formation of the American Radium Society. Editorial. Am. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1953, 70, 487-491.

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<sup>7</sup> Resolution of the American Radium Society at Its Sixth Annual Meeting, June 6, 1921, Boston, Massachusetts. Am. J. ROENTGENOL., 1921, 8, 490.

8 SCHMITZ, H. Development of forms of treatment in carcinoma of uterine cervix during last one-hundred years; Janeway Lecture, 1938. Am. J. ROENTGENOL. & RAD. THERAPY, 1938, 40, 805–816.

ing of such a Lecture as the central theme of the Annual Meeting. Their motion to this effect was adopted by the American Radium Society and the first Janeway Lecture was presented by James Ewing, a friend of Janeway, before the American Radium Society, during the American Congress of Radiology, September 25–30, 1933. Dr. Lee could not attend because of illness and his untimely demise occurred November 10, 1933.

While the Janeway Lecture continued, as intended, to be the outstanding event of every succeeding Annual Meeting, the Janeway Medal, the Society's highest mark of recognition, which is awarded to the Lecturer, was not struck until 1937, largely through the efforts of Dr. Edward H. Skinner. 10 The medal was designed by Miss Stephanie Prince of Kansas City, Missouri, and executed by Tiffany of New York. A replica was presented to each of the Lecturers from 1933 to 1937 at an evening meeting devoted to the American Radium Society during the sessions of the Fifth International Congress of Radiology held in Chicago, Illinois, in 1937 and since then has been presented to the Janeway Lecturer at every Annual Meeting.

The subject chosen for this Medal was taken from Norse mythology and most appropriately symbolizes the sacrifice of those who have worked with radium. According to the legend, "Odin, the ruler of the Gods, having wandered over the earth in search of knowledge, finally came to Mimir's well in whose waters wisdom and wit lay buried. But the price asked for a drink from the well was Odin's right eve. So Odin plucked out his eve and gave it to Mimir for a potion of wisdom." On the reverse side of the Medal are two ravens which Odin possessed, "Hugin (thought or reflection) and Munin (memory or remembrance). The ravens perched upon his shoulders. To them he owed a great part of

EWING, J. Early experience in radium therapy. Am. J. ROENT-GENOL. & Rad. Therapy, 1934, 37, 153-190.
 SKINNER, E. H. The Henry Harrington Janeway Lecture and

<sup>19</sup> SKINNER, E. H. The Henry Harrington Janeway Lecture and Medal. Editorial. Am. J. Roentgenol. & Rad. Therapy, 1938, 40, 626–628.

his wisdom for each day they flew forth through the expanses of the universe returning to tell him of all they had seen and reported upon the events and progress of the world."

Allegorically, the events and progress in the expanses of the ionizing radiations are faithfully reflected in the brilliant array of the 30 Janeway Lectures delivered as the highlights of the American Radium Society Annual Meetings from 1931 to 1965. The JOURNAL considers itself extremely fortunate in having been able to publish—with the exception of the 2nd, 20th and 27th—all Lectures, thereby significantly enhancing the already high standard of its scientific facet.

An important event in the late 1940's was the impact of the artificially created radioactive isotopes on radiology, both diagnostic and therapeutic. After careful deliberations at several successive meetings, the American Roentgen Ray Society, at the September, 1951, meeting held in Washington, D. C., "recognized the increasing importance of radioisotopes in diagnostic procedures and as therapeutic agents" and the term of "Nuclear Medicine" was added to the title of the JOURNAL in order to connote the interest in atomic medicine.11 Thus, the name of the JOURNAL became The American Journal of ROENTGENOLOGY, RADIUM THERAPY & NU-CLEAR MEDICINE, which has remained the same since then.

The American Radium Society, for similar reasons, felt that a new expression of purpose was needed in its constitution and the members in 1950 decided to change the objective of the Society as stated in the original constitution to read: "The objective of the Society shall be to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties and their therapeutic application."

<sup>11</sup> Addition to title of Journal. Editorial. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1952, 67, 114.

In 1961, yet a third change<sup>12</sup> was made in the statement of objectives in the constitution of the American Radium Society, which now reads: "The objectives of the Society shall be to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties, their biologic effect, and their therapeutic application; and to encourage liaison between the various specialties concerned with the treatment of cancer."

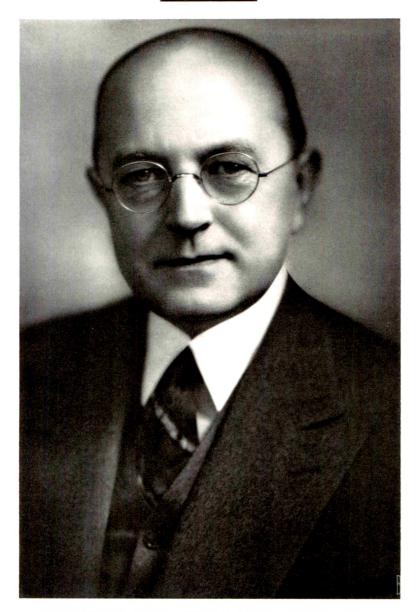
In view of the fact that the Journal, founded as The American Quarterly of Roentgenology, has been the official organ of the American Roentgen Ray Society since 1906, and of the American Radium Society since 1920, all of the submitted articles of these two great Societies were regularly published on its pages. In addition, many other independently submitted original articles were published, together with abstracts of domestic and foreign radiologic literature, editorials, obituaries, book reviews, accounts of the Annual Meetings of both Societies, reports and bulletins of National and International organizations, particularly on radiation protection and safety, and many other items of scientific, educational and organizational interest.

This enormous material has also been carefully compiled, thoroughly indexed and cross-indexed, and published in 6 volumes of Consolidated Indices, thereby facilitating a rapid chronologic and historic perusal of the events and progress recorded.

On this festive occasion of the Golden Anniversary, the Editorial Staff of the Journal expresses a deep sense of gratitude to the American Radium Society for its splendid cooperation and extends its congratulations for a monumental achievement of scientific advancement.

T. LEUCUTIA, M.D.

<sup>&</sup>lt;sup>12</sup> Brown, R. L. Objectives of American Radium Society; President's address, 1962. Am. J. ROENTOENOL., RAD. THERAPY & NUCLEAR MED., 1963, 89, 3-5.



FREDERICK WILLIAM O'BRIEN 1881-1965

THE sudden death of Fred 5 December 20, 1965, after a brief illness to HE sudden death of Fred O'Brien on is freighted with a special sense of loss to New England, which he served outstandingly for many years and on a far wider scale through the strong support he loaned to organized radiology across the nation. In a particular sense, Dr. O'Brien's death

marked the end of an era regionally. He was one of the founders, in 1919, of the New England Roentgen Ray Society and the last surviving charter member of that organization.

A native of Boston and a graduate of its public schools, Dr. O'Brien attended St. Andrew's in Poughkeepsie, New York, and

Woodstock College in Maryland. He was graduated from Tufts College Medical School in Boston in 1911. A Bachelor of Arts degree was conferred upon him by Boston College in 1920, and in 1948 he received an honorary Doctor of Laws degree from the same institution. His early preparation in Radiology included studies in Vienna and courses in Radiation Physics and Biophysics at the Jefferson Physical Laboratory of Harvard. An active practitioner of Radiology throughout his life, even to within a few days of his death, he was also recognized as an outstanding academic radiologist of his period. He served as Instructor, Assistant Professor, and Associate Professor of Roentgenology, and Professor of Radiology at Tufts Medical School. He was visiting roentgenologist and consultant in Radiology to the Boston City Hospital from 1926 to 1949 and Director of the New England Medical Center, Department of Radiology, 1930-1940. In addition he served as an active roentgenologist and consultant to many other local hospitals within the area.

That Dr. O'Brien's qualifications were recognized by his colleagues is apparent from the list of offices he held and the honors which were bestowed upon him. He was President of the New England Roentgen Ray Society in 1924-1925 and was Chairman of the Section on Radiology of the Massachusetts Medical Society in 1927-1928. As President of the American Radium Society in 1940–1941 and President of the Radiological Society of North America in 1947-1948, he exemplified his broad contribution to our specialty. He was a Trustee of the American Board of Radiology from 1942 to 1964, and was a Chancellor of the American College of Radiology. Granting of the Janeway Medal of the American Radium Society in 1946 and the Gold

Medal of the Radiological Society of North America in 1959 signified the esteem of his peers.

As an officer of the various societies which he served, Dr. O'Brien was distinguished for his precise and concise thinking. As a Trustee of the American Board of Radiology, a position which is of critical significance, he displayed astuteness and fairness of the highest degree. Generous, firmly gentle, always a gentleman—of how many can this be said?

Fred O'Brien's interests in Radiology were broad throughout his life. His major interest, however, was radiation therapy, and he is to be classed as one of the early radiation therapists of America. His interest and his attitudes tended to strengthen the position of radiation as a therapeutic agent in the New England area and throughout the nation. Beloved by his students, by his residents, and, above all, by his patients, he made a distinctive mark on the landscape of radiation therapy in this country—a significant attainment for the period in which he lived and worked.

Dr. O'Brien is survived by his wife, Sarah; a daughter, Marie Therese Foley of Rye, New York; and two sons, both radiologists continuing the family tradition—Frederick W., Jr., of Bakersfield, California, and Richard G. of Boston.

Not only has Radiology lost a great benefactor in the death of Dr. O'Brien, but a true gentleman has been called from our ranks. He needed no external mark of distinction, but a white carnation in his lapel was so much a part of him that his many friends and colleagues will be glad to know that one went with him to his grave.

LAURENCE L. ROBBINS, M.D.

Massachusetts General Hospital Boston, Massachusetts 02114



ROBERT REID NEWELL, M.D. 1892–1965

DR. ROBERT REID NEWELL—scholar, physician, teacher, scientist, writer, man of warm heart and understanding, died at his home on August 28, 1965. With his passing was lost a great and inquiring mind, a wonderful sense of humor, and one who wore his justly-earned halo with humility.

He is survived by his widow, the former Jeannette LeValley, his son, Dr. Allen Newell at Carnegie Institute of Technology in Pittsburgh, and his daughter, Mrs. Ann McKnight of Hatfield, Pennsylvania.

Dr. Newell was a native Californian, born in Stockton. He had his undergraduate and medical school training at the University of California, where he was elected to both Phi Beta Kappa and Alpha Omega Alpha. He took his internship and residency in radiology at the same institution.

He became an Instructor in Radiology at the Stanford University Medical School in 1920, and rose to be Professor of Radiology and Director of the Department in 1932. In addition, he held the title of Professor of Medicine in Biophysics and Director of the Isotope Laboratory until his compulsory retirement at the age of 65.

Dr. Newell then undertook another career as consultant with the Naval Radiologic Defense Laboratory at Hunter's Point, a post he held until the onset of his final illness a few months ago. At the Laboratory, he enjoyed a position given to few men and was able to exercise his vast fund of knowledge, ingenuity, and powers of reasoning in working directly with the personnel in all their various fields of endeavor.

During Dr. Newell's extremely active career, he was the author of over 90 scientific papers ranging in subject from diagnostic and therapeutic radiology, radioisotopes, mathematics, and physics, to philosophic concerns such as "Mink Coats and Cadillacs: A Discourse on the Nutri-

tion and Hygiene of the Soul," and "Pain and Cruelty."

He did pioneer work in supervoltage radiation therapy, the x-ray study of vision, the clinical use of radioisotopes, the early study of gallbladder radiography, studies of error in the roentgen interpretations of chest films, radiation dosage and the effect of radiation on man.

Dr. Newell held membership in 36 professional and nonprofessional societies. He was elected President of the California Academy of Medicine and was both President and Gold Medalist of the American College of Radiology. He also received the Gold Medal of the Radiological Society of North America.

One of the great joys of his life was made up of those times he spent at the Lake of the Woods in the high Sierras. Here he was the ardent fisherman, mountaineer, and raconteur.

The world has lost a great man with the passing of Robert Reid Newell.

EARL R. MILLER, M.D.

Department of Radiology School of Medicine University of California San Francisco Medical Center San Francisco, California 94122



# **NEWS ITEMS**

# WORKSHOP IN RADIOISOTOPE SCANNING EMORY UNIVERSITY

Emory University School of Medicine announces a 5½ day workshop in principles, techniques, and interpretation of Radio-isotope Scanning to be held April 11–16, 1966, in Atlanta, Georgia.

This course is limited to individuals who have had previous experience with radioisotopes and who wish to add or extend scanning procedures to their diagnostic service.

Participants will work with phantoms and patients on a variety of scanning units to develop familiarity with various units and various radioisotopes and the parameters of scan interpretation. Extensive teaching files will be available for study. A series of lectures covering principles, indications and interpretation of scans will be presented by a select panel.

For further information contact Joseph L. Izenstark, M.D., Division of Nuclear Medicine, Department of Radiology, Emory University School of Medicine, Atlanta, Georgia 30382.

# SAN DIEGO BIOMEDICAL ENGINEERING SYMPOSIUM

The 1966 San Diego Nuclear Biomedicine Seminar will be held March 18–19, 1966 in San Diego, California, at the Kona Kai Club on Shelter Island.

The Seminar is titled "Current Nuclear Applications in Medicine and Biology: Problems, Advances, and Progress Reports."

The Program Chairman is Frederick W. George, III, Captain (MC), USN, Head, Radioisotopes—Radiation Therapy Section, U. S. Naval Hospital, San Diego.

For further information contact J. M.

Hlavin, Registration Chairman, P. O. Box 2228, La Jolla, California.

# COURSE IN GASTROINTESTINAL ROENTGENOLOGY INDIANA UNIVERSITY

The Department of Radiology of Indiana University School of Medicine announces a postgraduate course March 29–April 1, 1966. The course is planned primarily for the general radiologist but is open to all physicians having an interest in this field. Presentations will consist of lectures, film interpretation conferences, and exhibits correlating the radiologic, pathologic, and physiologic aspects of various gastrointestinal conditions encountered in clinical practice.

The course will be presented by the faculty of Indiana University and the following guest participants: Stanley Baum, Philadelphia, Pennsylvania; Harley C. Carlson, Rochester, Minnesota; Steven I. Figiel, Detroit, Michigan; John R. Hodgson, Rochester, Minnesota; Albert Jutras, Montreal, Canada; Richard H. Marshak, New York City, New York; Harry Z. Mellins, Brooklyn, New York; Sidney Nelson, Columbus, Ohio; Seymour F. Ochsner, New Orleans, Louisiana; Leo Rigler, Los Angeles, California; Francis F. Ruzicka, Jr., New York, New York; Richard Schatzki, Cambridge, Massachusetts; Everett H. Schultz, Jr., Chapel Hill, North Carolina; George N. Stein, Philadelphia, Pennsylvania; Jerry Wiot, Cincinnati, Ohio; Robert E. Wise, Boston, Massachusetts; and Bernard Wolf, New York City, New York.

Fur further information, write the Director of Postgraduate Medical Education, Indiana University School of Medicine, Indianapolis, Indiana 46207.



# **BOOKS RECEIVED**

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

# BOOKS RECEIVED

IL CESIO 137 IN RADIOTERAPIA, By R. Miceli, A. Corinaldesi, and C. Rimondi, Istituti di Radiologia e del Radio, Università Di Bologna. Cloth. Pp. 224, with many illustrations. Price, L. 5,000. Edizioni Minerva Medica, Torino, Italy, 1963.

L'Immagine Radiologica Amplificata: Basi e METODI DI OSSERVAZIONI. By Renzo Bossi, and Francesco Coucourde. Cloth. Pp. 218, with many illustrations. Price, L. 8,000. Edizioni Minerva

Medica, Torino, Italy, 1965. Das Röntgenfernsehen: Technische Grund-LAGEN UND KLINISCH-RÖNTGENOLOGISCHE AN-WENDUNG. By Prof. Dr. Alfred Gebauer, Leiter der Röntgenabteilung der Medizinischen Kliniken der Universität Frankfurt am Main; Prof. Dr. Josef Lissner, Oberarzt der Klinik für Strahlentherapie und Nuklearmedizin der Universität Frankfurt am Main; and Dipl.-Ing. Ottfried Schott, Leiter des Grundlagenlabors der Röntgenentwicklung und wissenschaftlicher Berater Siemens-Reiniger-Werke AG, Erlangen. Paper. Pp. 164, with 92 illustrations. Price, DM 34.-. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart 1, Germany, 1965.

Principles of Bone X-Ray Diagnosis. Second edition. By George Simon, M.D., F.R.C.P., F.F.R., Assistant Director, X-ray Department, Brompton Hospital, London; Radiologist, St. Bartholomew's Hospital, London; Demonstrator, Radiological Anatomy, St. Bartholomew's Hospital, London; Curator of the Radiological Museum and Teacher of Radiology, The Institute of Diseases of the Chest, University of London, London, England. Cloth. Pp. 193, with many illustrations. Price, \$13.25. Butterworth Inc., 7300 Pearl Street, Washington 14, D. C., 1965.

FERMENT IN MEDICINE: A STUDY OF THE ESSENCE OF MEDICAL PRACTICE AND OF ITS NEW DILEMMAS. By Richard M. Magraw, M.D., Professor, Departments of Internal Medicine and Psychiatry, University of Minnesota; Director, Comprehensive Clinic Program, University of Minnesota Medical School. With a chapter on Automation in Medicine written in collaboration with Daniel B. Magraw, M.B.A. Cloth. Pp. 272. Price, \$6.50. W. B. Saunders Company, West Washington Square, Philadelphia, 1966.

THE EARLY RADIOLOGICAL DIAGNOSIS OF DISEASES OF THE PANCREAS AND AMPULLA OF VATER. Elective exploration of the ampulla of Vater and the head of the pancreas by hypotonic duodenography. By Paul Jacquemet, M.D., Chief of Radiological Laboratory, Lyon Faculty of Medicine and Affiliated Hospitals, Lyon, France; Domingo Liotta, M.D., Assistant Professor of Surgery, Baylor University College of Medicine, Houston, Texas; and Pierre Mallet-Guy, M.D., F.A.C.S. (Hon.), Professor of Surgery, Lyon Faculty of Medicine, Lyon, France. Translated by Lee D. Cady, M.D., F.A.C.P., F.A.C.H.A., Emeritus Professor of Medical Administration, Baylor University College of Medicine, Houston, Texas. Cloth. Pp. 238, with many illustrations. Price, \$14.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1965.

Annual Review of Nuclear Science. Volume 15. Emilio Segrè, Editor, University of California, Berkeley; Gerhart Friedlander, Associate Editor, Brookhaven National Laboratory; and H. Pierre Noyes, Associate Editor, Stanford University. Cloth. Pp. 502, with some illustrations. Price, \$8.50. Annual Reviews, Inc., 231 Grant Avenue,

Palo Alto, Calif., 1965.

HUMAN PATHOLOGY: AN INTRODUCTION TO MEDI-CINE. By Robert P. Morehead, B.S., M.A., B.S.Med., M.D., F.A.C.P., F.C.A.P., Professor of Pathology and Chairman of the Department of Pathology, The Bowman Gray School of Medicine of Wake Forest College; Chief of Pathology, The North Carolina Baptist Hospital; and Pathologist to The Medical Center. Cloth. Pp. 1,676, with many illustrations. Price, \$23.50. McGraw-Hill Book Company, 330 West 42nd Street, New York, N. Y., 1965.

Präsenile Osteoporose: Physiologie des Knoch-ENUMBAUS UND MESSUNG DER SPONGIOSADICHTE. By Doz. Dr. Heinz Wagner, Orthopädische Universitätsklinik und Poliklinik, (Hüfferstiftung) Münster/Westf., with a forward by Prof. Dr. Oskar Hepp, Münster/Westf. Paper. Pp. 147, with 58 illustrations. Price, DM 39.-. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart 1, Germany, 1965.

XITH INTERNATIONAL CONGRESS OF RADIOLOGY. September 22-28, 1965, Rome. International Congress Series, No. 89. Paper. Pp. 532. Price, \$15.00. Excerpta medica Foundation, 119-123 Herengracht, Amsterdam, The Netherlands, 1965.

THE RADIOLOGIC CLINICS OF NORTH AMERICA. Symposium on Radiologic Techniques in the Detection of Primary and Metastatic Cancer. David M. Sklaroff, M.D., Guest Editor, Cloth. Pp. 279, with many illustrations. December, 1965, Volume III, Number 3. W. B. Saunders Company, West Washington Square, Philadelphia, 1965.

Surgical Treatment of Spondylolisthesis Without Spine Fusion: A Long Term Follow-up of Operated Cases. By Gerald G. Gill, M.D., and Hugh L. White, M.D., San Francisco, Calif. Paper. Pp. 99, with many illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 85. Munksgaard, Copenhagen, 1965.

Cona Plana: A Clinical and Radiological Investigation with Particular Reference to the Importance of the Metaphyseal Changes for the Final Shape of the Proximal Part of the Femur. By Walter Edgren. Paper. Pp. 129, with some illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 84. Munksgaard, Copenhagen, 1965.

A Rheologic Model for Cortical Bone: A Study of the Physical Properties of Human Femoral Samples. By Elias D. Sedlin. Paper. Pp. 77, with some illustrations. Acta Orthopaedica Scandinavica, Supplementum 83. Munksgaard, Copenhagen, 1965.

HAEMOPHILIA IN SWEDEN. VII. INCIDENCE, TREATMENT AND PROPHYLANIS OF ARTHROPATHY AND OTHER MUSCULO-SKELETAL MANIFESTATIONS OF HAEMOPHILIA A AND B. By Åke Ahlberg. Paper. Pp. 132, with many illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 77. Munksgaard, Copenhagen, 1965.

The Pulmonary Circulation During Pneumonia: A Cinedensigraphic Study. By Carl-Gustaf Standertskjöld-Nordenstam. Paper. Pp. 123, with some illustrations. Acta Radiologica, Supplementum 239. Acta Radiologica, Stockholm 2, Sweden, 1965.

GRANULOCYTE DISTRIBUTION IN BONE MARROW, BLOOD AND DIFFERENT ORGANS IN WHOLE BODY IRRADIATED RATS, By Antti Cederberg, Paper, Pp. 94, with some tables. Acta Radiologica Supplementum 240. Acta Radiologica, Stockholm 2, Sweden, 1965.

DECORPORATION OF RADIOSTRONTIUM: RADIOACTIVE

Assay Techniques: An Experimental Study on Mice. By Kai Setälä. Paper. Pp. 61, with some illustrations. Acta Radiologica Supplementum 241. Acta Radiologica, Stockholm 2, Sweden, 1965.

Conformation Radiotherapy: Rotation Techniques as Applied to Radiography and Radiotherapy of Cancer. By Shinji Takahashi. Paper. Pp. 142, with many illustrations. Acta Radiologica, Supplementum 242. Acta Radiologica, Stockholm 2, Sweden, 1965.

RADIOACTIVE BISMUTH <sup>206</sup>Bi: EXPERIMENTAL STUD-IES AND CLINICAL APPLICATIONS. By J. Th. van der Werff. Paper. Pp. 89, with some illustrations. Acta Radiologica Supplementum 243. Acta Radiologica, Stockholm 2, Sweden, 1965.

Effects of Ionizing Radiation on Creatine Metabolism in Patients Treated for Malignancy and in Rats. By Samuel S. Kurohara. Paper. Pp. 125, with some illustrations. Acta Radiologica Supplementum 244. Acta Radiologica, Stockholm 2, Sweden, 1965.

RADIOLOGY OF THE DIGESTIVE SYSTEM: A RADIOLOGICAL COMPANION TO TRUELOVE AND REYNELL'S DISEASES OF THE DIGESTIVE SYSTEM. BY K. Lumsden, M.A., M.B., B.Chir., D.M.R.E., Consultant Radiologist, Radeliffe Infirmary, Oxford; Clinical Lecturer in Radiology, University of Oxford; and S. C. Truelove, M.A., M.D., F.R.C.P., Nuffield Department of Clinical Medicine, University of Oxford. Cloth. Pp. 548, with 530 illustrations. Price, \$22.50. F. A. Davis Co., 1914–16 Cherry Street, Philadelphia, Pa., 1965.

X-RAY PHYSICS AND EQUIPMENT. By F. Jaundrell-Thompson, Principal Superintendent Radiographer, The Royal Hospital of St. Bartholomew, London; Honorary Fellow and Past President, Society of Radiographers; and W. J. Ashworth, Superintendent Radiographer/Teacher Principal, Bromley Hospital, Bromley, Kent; Honorary Fellow and Past President, Society of Radiographers. Cloth. Pp. 811, with 383 illustrations. Price, \$16.50. F. A. Davis Co., 1914–16 Cherry Street, Philadelphia, Pa., 1965.

It is with deep regret that we announce the death on January 30, 1966, in Utica, New York, of Dr. Douglas A. Quick, Past President of the American Radium Society and Life Member of the American Roentgen Ray Society.



# SOCIETY PROCEEDINGS

# MEETINGS OF RADIOLOGICAL SOCIETIES\*

#### United States of America

American Roentgen Ray Society

Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: San Francisco Hilton Hotel, San Francisco, Calif., Sept. 27–30, 1966.
American Radium Society

Secretary, Dr. John L. Pool, 444 East 68th Street, New York, N. Y. 10021. Annual meeting: Camelback

Inn, Phoenix, Ariz., April 13-16, 1966 (Golden Anniversary).

RADIOLOGICAL SOCIETY OF NORTH AMERICA

Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744

South Fifty-eighth St., Lincoln, Neb. Annual meeting:
Palmer House, Chicago, Ill., Nov. 27-Dec. 2, 1966.

AMERICAN COLLEGE OF RADIOLOGY

The College of Radiology

Strength 20 N Wacker

Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Beverly Hilton

Hotel, Los Angeles, Calif., Jan. 21-Feb. 4, 1967. Section on Radiology, American Medical Association Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: Chicago, Ill., June 26-30, 1966.

American Board of Radiology

Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1966 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 6-10, inclusive. The deadline for filing applications for this examination

was December 31, 1965.

The Fall 1966 examination will be held at the Washington Hilton Hotel, Washington, D.C., December 5-9, inclusive. The deadline for filing applications is June 30,

American Association of Physicists in Medicine Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

American Club of Therapeutic Radiologists Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo.

ELEVENTH INTERNATIONAL CONGRESS OF RADIOLOGY
Secretary-General, Professor Dr. Med. Arduino Ratti, via Moscova, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy.

Ninth Inter-American Congress of Radiology Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania. President, Dr. Leandro Zubiaurre, Montevideo, Uruguay. Meeting: Montevideo, Uruguay, 1967. Inter-American College of Radiology

President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

ALABAMA RADIOLOGICAL SOCIETY

Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

American Nuclear Society

Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.

ARIZONA RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF AMERICAN COLLEGE OF RADIOLOGY

Secretary-Treasurer, Dr. James R. Morrison, 550 S. University, Little Rock, Ark, 72205.

Arkansas Radiological Society

Secretary, Dr. Charles W. Anderson, 11081 Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists

Secretary-Treasurer, Dr. Morton M. Kligerman, Dept. of Radiology, Yale University Medical School, New Haven, Conn. Annual meeting: University of Arkansas, Little Rock, Ark., May 13-14, 1966.

ATLANTA RADIOLOGICAL SOCIETY

Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN.-AMERICAN RADIOLOGIC SOCIETY

Secretary, Dr. Roy R. Deffebach, Major, MC, Radiology
Service, 5th General Hospital, APO 154, New York, N. Y.

Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. R. John Gould, 441 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Arthur Lieber, University of Kentucky, University Hospital, Lexington, Kentucky. Meets quarterly.

BROOKLYN RADIOLOGICAL SOCIETY Secretary, Dr. Edward Feely, St. Johns Episcopal Hospital, 480 Herkimer St., Brooklyn, N. Y. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Munschauer, 130 Hodge Ave., Buffalo, N.Y. 14222. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY

Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.

CATAWBA VALLEY RADIOLOGICAL SOCIETY Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Tuesday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C. at 12:00 P.M.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month, October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Atis K. Freimanis, Ohio State Univ. Hospitals, 410 W. 10th Ave., Columbus, Ohio 43210. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE

Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY Secretary-Treasurer, Dr. Robert D. Moseley, Jr., Dept. of Radiology, Univ. of Chicago, 950 E. 59th St., Chicago 37, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at

CLEVELAND RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. James Christie, 10515 Carnegie

<sup>\*</sup> Secretaries of societies are requested to send timely information promptly to the Editor.

Avenue, Cleveland, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

COLORADO RADIOLOGICAL SOCIETY

Secretary, Dr. George F. Wertz, 1801 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY

Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY Secretary, Dr. R. E. Collier, 3500 Gaston Ave., Dallas, Tex. Meets monthly, third Monday, at Southwest International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society

Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit

1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY

Secretary, Dr. William G. Faraghan, 450 30th St., Oakland 9, Calif. Meets first Thursday each month at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. C. H. Kimball, 2200 Harris Circle, Cleveland, Tenn. Meets in January and September. EASTERN RADIOLOGICAL SOCIETY

Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

GEORGIA RADIOLOGICAL SOCIETY

Secretary, Dr. I. R. Berger, 1010 Prince Ave., Athens, Ga. Meets in spring and fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Arthur R. Miller, North Miami General Hospital, 1701 N.E. 127th St., North Miami, Fla. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS Secretary-Treasurer, Dr. Mark D. Eagleton, 950 Francis

Place, St. Louis, Mo. HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. William A. Vint, 1004 Seymour, Pasadena, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

IDAHO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.

Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY

Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Home, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER, AMERICAN COLLEGE OF RADIOLOGY Secretary-Treasurer, Dr. Robert H. Greenlaw, Dept. of Radiology, Univ. of Kentucky Med. Ctr., Lexington, Ky. Meets semiannually.

KENTUCKY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY

Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY

Secretary, Dr. David Faegenburg, Nassau Academy of Medicine, 1200 Stewart Ave., Garden City, L. I., N. Y. 11533. Meets second Tuesday of the month in February, April, June, October and December. Los Angeles Radiological Society

Secretary, Dr. Joseph A. Parks, 15107 Vanowen St., Van Nuys, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

MAINE RADIOLOGICAL SOCIETY

Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Waterville, Me. Meets in June, September, December and April .

MARYLAND RADIOLOGICAL SOCIETY

Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Md.

Memphis Roentgen Society

Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Alexander W. Friedman, Mid-Hudson Medical Group, Fishkill, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY Secretary-Treasurer, Dr. Donald P. Babbitt, 1700 W. Wisconsin Ave., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Edward A. Peterson, St. Paul, Minn. Meets twice annually, fall and winter.

MISSISSIPPI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MISSOURI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

MONTANA RADIOLOGICAL SOCIETY

Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

NEBRASKA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY

Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

NEW ENGLAND ROENTGEN RAY SOCIETY

Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month, October through April, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists

Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico. New Mexico Society of Radiologists

Secretary, Dr. William G. McPheron, Hobbs, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW YORK ROENTGEN SOCIETY

Secretary, Dr. Milton Elkin, Albert Einstein College of Medicine, Bronx, N.Y. 10461. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Meeting: Waldorf-Astoria Hotel, N. Y., April 21-23, 1966.

NORTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

NORTH DAKOTA RADIOLOGICAL SOCIETY

Secretary, Dr. Robert J. Olson, 1240 8th Ave., Williston, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. John Turner, 1215-28th St., Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento. NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society

Secretary, Dr. Mortimer Lubert, Cleveland, Ohio. Annual meeting: Toledo, Ohio, May 13-15, 1966.

OKLAHOMA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Robert Sukman, 1200 N. Walker, Oklahoma City, Okla. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. George W. Logan, 301 Newport Blvd., Newport Beach, Calif. Meets fourth Tuesday of every month in Orange County Medical Association Build-

Oregon Radiological Society

Secretary-Treasurer, Dr. Robert S. Miller, 13753 S.W. Farmington Rd., Beaverton, Ore. 97005. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month. Pacific Northwest Radiological Society

Secretary-Treasurer, Dr. Willis Taylor, 1118 9th Ave. Seattle, Washington. Annual meeting to be announced.

PENNSYLVANIA RADIOLOGICAL SOCIETY

Secretary, Dr. T. Frederick Weiland, Jr., 619 Ridgeway Ave., Grove City, Pa. Annual meeting: Hotel Hershey, May 12-14, 1966.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY

Secretary, Dr. Robert N. Berk, 3305 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SOCIETY OF CONNECTICUT, INC. Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450

Chapel St., New Haven 11, Conn. Meetings are held quarterly.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI Secretary, Dr. Harold N. Margolin, 6159 Tulane Road, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF HAWAII Secretary-Treasurer, Dr. Robert W. Edland, P.O. Box 282, USA Tripler General Hospital, Honolulu, Hawaii.

Meets third Monday of each month at 7:30 P.M. RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA

Secretary, Dr. Lester W. Eavenson, 2700 Napoleon Ave., New Orleans 15, La. Meets semiannually, during Lou-siana State Medical Society meeting and 6 months later.

RADIOLOGICAL SOCIETY OF NEW JERSEY Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA Secretary-Treasurer, Dr. Gerald M. McDonnel, U.C.L.A. Medical Center for Health Sciences, Los Angeles, Calif. 90024. Meets three times a year, usually October, February, and May.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y. Secretary, Dr. Irving B. Joffe, Rochester General Hospital, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 18–20, 1966.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Charles P. Hyslop, 7901 Frost St., San Diego 22, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society

Secretary, Dr. Malcolm Jones, University of California Hospital, San Francisco 22, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the Dis-TRICT OF COLUMBIA

Secretary-Treasurer, Dr. George T. Hennessey, Washington, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 р.м.

Section on Radiology, Southern Medical Association Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. Annual meeting: Washington, D. C., Nov. 14-17, 1966. Section on Radiology, Texas Medical Association

Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: San Francisco Hilton Hotel, San Francisco, Calif., Sept. 26, 1966.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National
Laboratories, Oak Ridge, Tenn. Administrator, Mr.
Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting to be announced.

SOUTH BAY RADIOLOGICAL SOCIETY

Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Carleton J. Wright, 2015 Clarman Way, San Jose, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTH DAKOTA RADIOLOGICAL SOCIETY

Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

SOUTHERN RADIOLOGICAL CONFERENCE

Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting to be announced.

SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. E. K. Carter, Holston Valley Community Hosp., Kingsport, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting to be announced.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgen-OLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY

Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Carlisle C. Smith, Salt Lake Genera Hospital, 2033 S. State St., Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY

Secretary, Dr. John R. Williams, 160 Allen St., Rutland,

VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

Washington State Radiological Society

Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. Karl J. Myers, The Myers Clinic-Broad-dus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee. Westchester Radiological Society

Secretary, Dr. Peter P. Brancucci, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society

Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. Meets twice a year, May and September.

Wyoming Radiological Society

Secretary, Dr. Ronald R. Lund, 240 W. 9th St., Casper, Wyo. Meets in fall with State Medical Society and in spring on call of President.

### CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá. Secretary-General, Dr. Roberto Calderón, Calle Central

Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala

Secretary, Dr. Carlos E. Escobar, 92. Calle A 0-05, Zona 1 Guatemala.

Sociedad de Radiología y Fisioterapía Cubana

Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia

Secretary, Dr. James Fernández Carballo, Apartado VIII San José, Costa Rica.

Sociedad Mexicana de Radiología, A.C.

Calle del Oro No. 15, México 7, D. F. Secretary-General, Dr. E. Alvarez Hernández.

Meets first Monday of each month. Asociación Puertorriqueña de Radiología

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting. Sociedad Radiológica de Puerto Rico

Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

#### British Commonwealth of Nations

Association of Radiologists of the Province of Quebec Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. I, England. Meets monthly from October until May. Annual Meeting: School of Pharmacy, Brunswick Sq. 29-39, London, Mar. 31-Apr. 1, 1966.

Canadian Association of Physicists, Division of Medical and Biological Physics.

Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario London, Ont., Canada. Annual meeting to be announced.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY Secretary, Dr. B. V. Evans, 105 Northgate Bldg., Alberta, Canada. Meets second Tuesday of each month in various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS

Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS IN IRELAND

Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MED: CINE (CONFINED TO MEDICAL MEMBERS)

Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, I Wimpole St., London, W. I, England.

Canadian Association of Radiologists

Honorary Secretary-Treasurer, Dr. D. J. Sieniewicz, Associate Honorary Secretary-Treasurer, Dr. Maurice Dufresne, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Queen Elizabeth Hotel, Montreal, March 2-6, 1966.

MONTREAL RADIOLOGICAL STUDY CLUB

Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie Secretary General, Dr. Jacques Lespérance, 1656 Sherbrooke East, Montreal, Que., Canada. Meets every third Tuesday from October to April. Annual meeting to be announced.

TORONTO RADIOLOGICAL SOCIETY

Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia

Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

#### SOUTH AMERICA

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.
ATENEO DE RADIOLOGIA

Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario. Colégio Brasileiro de Radiologia

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil

Sociedad Argentina de Radiologia

Secretary, Dr. Edwarde A. Navarrine, Santa Fe 1171, Buenos Aires, Meetings are held monthly.

Sociedad Bolivana de Radiología

Secretary, Dr. Javier Prada Mendez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia

Secretary, Dr. Armando Uribe, Hospital Miltar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Écuatoriana de Radiología y Fisioterapía Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia

Secretary, Dr. Vicente Ubillus, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima. Sociedad de Radiologica del Atlantico

Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física MÉDICA DEL URUGUAY

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada

1464, piso 13, Montevideo, Uruguay. Sociedade de Radiologia de Pernambuco

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife,

Caixa Postal 505, Pernambuco, Brazil. Sociedad de Roentgenologia y Medicina Nuclear de

LA PROVINCIA DE CÓRDOBA

Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología

Secretary-General, Dr. Luis F. Muro, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas

## CONTINENTAL EUROPE

OSTERREICHISCHE RÖNTGEN-GESELLSCHAFT

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie

General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September,

October, November and December.

Société Européenne de Radiologie Pédiatrique Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France. General Secretary, Dr. Ole Eklöf, P.O. Box, Stockholm 60,

Sweden. Annual meeting to be announced.

Société Française d'Électroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du NORD, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8°,

France.

ČESKOSLOVENSKÁ SPOLEČNOST PRO ROENTGENOLOGII A Radiologii Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July,

August and September. Annual general meeting. Deutsche Röntgengesellschaft

Secretary, Professor Dr. med. H. Lossen, Universitäts-

Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany. Società Italiana di Radiologia Medica e di Medicina Nucleare

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

NEDERLANDSE VERENIGING VOOR RADIOLOGIE

Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

SCANDINAVIAN ROENTGEN SOCIETIES

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear

Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid. Schweizerische Gesellschaft für Radiologie und

NUKLEARMEDIZIN (SOCIÉTÉ SUISSE DE RADIOLOGIE ET DE MÉDECINE NUCLÉAIRE) Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

#### ASIA

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby
Road, Bombay 1, India.

Indonesian Radiological Society

Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah 1, Diakarta, Indonesia.

# ABSTRACTS OF RADIOLOGICAL LITERATURE

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## ROENTGEN DIAGNOSIS HEAD

LLOYD, GLYN A. S. Phleboliths in the orbit. Clin. Radiol., Oct., 1965, 16, 339-346. (From: X-ray Department, Moorfields Eye Hospital, City Road, London, E.C. 1, England.)

The demonstration of phleboliths in the orbit is uncommon. The author was able to find a total of 19 previously reported cases. In this paper he records 5 additional cases collected over a period of 12 years. All of the 5 presented radiologically with phleboliths in the orbit or in adjacent parts of the skull.

Roentgenograms revealed enlargement of the orbit on the side affected in all 5 patients, and in 4 there was increase in soft tissue density. In 4 of the patients phleboliths were present within the orbit. In 2 patients phleboliths were found extra-orbitally. In 1 of these the phlebolith was intracranial, close to the sella, and in the other a phlebolith was noted in the cheek, close to the lateral wall of the maxillary sinus.

Phleboliths are formed by the organization of a thrombus. Hager (1958), stated that calcification occurs when the organized thrombus is wholly or in part deprived of blood. There are two lesions in the orbit which may result in phleboliths: hemangioma and orbital varices. Orbital hemangiomas may be capillary or cavernous. The diagnosis is suggested clinically by a slowly developing painless proptosis. The enlargement of the orbit seen on roentgen examination is due to increased intraorbital pressure. Phleboliths are rarely found in association with cavernous hemangiomas.—Samuel G. Henderson, M.D.

Stuart, Charles. Television fluoroscopy in cerebral pneumography. *Radiology*, Nov., 1965, 85, 927–928. (From: Perth Radiological Clinic, Perth, Western Australia.)

A simple method of employing closed-circuit television fluoroscopy in cerebral pneumography has been developed at the Royal Perth Hospital, Perth, Australia. The procedure has been in use for over 12 months, and its value merits description.

A standard screening unit with a 90/90 tilting table is used, equipped with a 9 inch image intensifier linked to a closed-circuit television unit. Spot roent-genograms are made whenever desired. The table is in vertical position for the procedure.

The patient is seated on a special chair fitted with shoulder and waist straps and an adjustable chin rest. The degree of flexion or extension of the head can be varied by the chin rest. The chair is placed in the lateral position against the vertical table, and the screening unit is aligned with the patient's head. A lumbar puncture is then performed, and 5 cc. of air is introduced initially. If the air collects in the cis-

terna magna the head can be gently manipulated, and the operator can watch the air proceed up the ventricular system. Filling of the ventricular system can be continued until the operator is satisfied. The whole procedure is viewed on the monitor, and if necessary, the patient can be swung around in the chair so that viewing in the posteroanterior position is possible. When filling is completed, the patient is placed on the table for the usual routine series of prone and supine roentgenograms.—Howard R. Stewart, M.D.

Shafron, Melvin, and Wiener, Stephen N. Pantopaque examination of the cerebellopontine angle. *Radiology*, Nov., 1965, 85, 921–926. (From: Mount Sinai Hospital, Cleveland, Ohio.)

Positive contrast examination of the cerebellopontine cisterns with ethyl iodophenylundecylate (pantopaque) injected via the lumbar route is a simple and effective method of demonstrating masses. It may prove the presence of a tumor which is not demonstrated on plain skull roentgenograms, making possible early and successful surgical correction. The procedure is an extension of cervical myelography. Special equipment is not required and spot roentgenograms are usually adequate for diagnosis. An accurate comparison of positive contrast cerebellopontine cisternography and pneumoencephalography is not the purpose of this article; rather, it is to stress that limited posterior fossa cisternography with pantopaque represents a practical method of tumor identification.

This procedure is most effectively performed by two operators. One is a fluoroscopist and the other controls and adjusts the position of the patient's head. Generally, 4-6 cc. pantopaque is injected into the lumbar area in the usual manner. With the patient prone and head hyperextended, the contrast agent is brought up to the cervical level by lowering head of the table. Controlled manual flexion of the patient's head will cause the pantopaque to flow cephalad and pool on the clivus, often making visible the basilar artery. Then, the head is turned obliquely a few degrees at a time under fluoroscopic guidance until it is lateral. The contrast agent then will outline the cerebellopontine angle. Spot roentgenograms are made, being sure to include the pantopaque in approximation to the medial aspect of the petrous bone and filling the internal auditory meatus.

The pantopaque can be kept within the posterior fossa and recovered almost entirely in the lumbar region if the following precautions are observed: (1) head motion should be entirely passive; (2) the pantopaque should not be allowed to course rostrally beyond the clivus before the head is turned; and (3) the vertex should not become dependent during the rotation of the head about its sagittal axis.

Both the normal and abnormal cisterns are ex-

amined in each patient. The contrast agent will flow back into the cervical region if the head is placed in the direct frontal, hyperextended position. The opposite cerebellopontine cistern is then recorded by repeating the appropriate rotation in the other direction.

After the examination is completed, the contrast agent is brought back down into the lumbar area by raising the head of the table to the erect position. Small drops of pantopaque that may be trapped in the lateral aspects of the cisterns may often be recovered by having the patient cough or shake his head gently.

Four cases in which this method was utilized to identify pontine angle tumors are presented. In 3 of these the plain skull roentgenograms were negative. In the other case there was confirmation and further definition of the tumor size. The cases are illustrated.—Paul M. Kroening, M.D.

#### NECK AND CHEST

Melvin, W. J. S., Dunlop, H. W., Hetherington, R. F., and Kerr, J. W. The role of the faceguard in the production of flexion injuries to the cervical spine in football. *Canad. M. A. J.*, Nov. 20, 1965, 93, 1110–1117. (From: Departments of Orthopedics, Neurosurgery and Traumatic Surgery, Queen's University and the Kingston General Hospital, Kingston, Ontario, Canada.)

The precise role of the single-bar face mask in producing major flexion violence to the cervical spine has been studied by a review of game movies, analysis of the roentgenograms and detailed interviews with 2 players who sustained fractures of the cervical spine.

This report is a suggestion for careful selection of a safe and efficient mask.

In the authors' opinion cervical spine injuries, although a potentially alarming complication of football, were extremely unusual. This opinion is shared by physicians attending all of the major intercol legiate and professional football teams in Canada.

The classic mechanism of neck injury in football, recognized as long as football has been played, is the direct impact of the head against an opposing player. Most typically these injuries occur during a misjudged tackle when the tackler, instead of putting his shoulder into the runner's legs, drives his head into the runner's knee.

A second mechanism of cervical spine injury has gained wide acceptance. The lesions in the cervical spines were typically those produced by major flexion violence.

The purpose of this communication is to draw attention to a third, undescribed mechanism of injury. In the 2 cases described, identical forces were applied to the cervical spine and remarkably similar lesions were produced in the vertebral column. In

both instances the player was tackled around the head, while running at full speed and bent forward; this had the effect of driving the runner headfirst into the ground. Each player was wearing a protruding single bar face mask attached to the helmet and the face-bar made first contact with the ground. The face mask was driven into the ground and fixed, thereby flipping the player's head into acute flexion as the momentum carried his trunk forward over the locked helmet. This mechanism is the exact opposite of that which produced hyperextension injuries, but, as with hyperextension injuries the faceguard appears to be a major factor in misdirecting the forces applied to the helmet.

The point of view as regards cervical spine injuries is that the helmet must fit extremely tightly. Only if the encircling webbing is tight, is the helmet efficient. In addition to the webbing, a chin strap ensures that the grasp of the helmet upon the head is extremely firm. All rotatory and angulatory strains applied to the helmet are unfortunately transmitted directly to the cervical spine. It is this firmness of grip which the authors believe is responsible for the translation of major forces to the cervical spine.

Some form of faceguard has recently been added because the basic helmet does not protect the face. Unfortunately, the more efficient the faceguard the heavier it is, and the more it tends to interfere with vision. The single-bar face mask which is slender to reduce weight, and which projects well out in front of the face to protect the nose and teeth, has been the decisive factor in the 2 flexion injuries described.

The escape of the cervical cord from injury appears to be due to the impingement of the face mask against the chest, which prevents further flexion displacement of the cervical spine.

A double bar, a broad bar, or a lineman's bird cage face mask all offer some degree of protection against overwhelming flexion violence. Face masks should be broad and should not project forward more than I inch beyond the tip of the nose in order to reduce their efficiency as cervical spine levers without interfering with their primary function of facial protection.

These injuries require the same management as similar injuries produced by other mechanisms. Like all cervical spine injuries, however, they are subject to deterioration, and progressive collapse of vertebral bodies, and/or an increasing laxity of ligaments often occurs.—Stephen N. Tager, M.D.

ROBERTSON, HUGH E. Pulmonary Alveolar proteinosis. Canad. M.A.J., Oct. 30, 1965, 93, 980–983. (Address: Director, Provincial Chest Clinic, Department of Health of Ontario, Suite 101, 353 Dalhousie Street, Ottawa 2, Ontario, Canada.)

Pulmonary alveolar proteinosis is a chronic disease of unknown etiology characterized by the deposition of proteinaceous and lipid material within the alveoli. This material appears to be produced from the alveolar lining cells which become necrotic and slough into the alveolar lumen.

The disease is predominant in males in a ratio of 3 to 1. Most of the patients described in the literature were adults between 20 and 50 years of age. Childhood cases are rare. Clinically, the disease presents with asymptomatic changes in the chest roentgenograms, progressive malaise, weight loss and dyspnea on effort; or with intermittent pneumonic illnesses causing cough, fever, purulent sputum and occasional hemoptysis. Physical signs of the chest are remarkably few. The only positive method of diagnosis at this time is lung biopsy.

Roentgenograms of the chest reveal flocculent, feathery or nodular pulmonary infiltrations extending outward from the hilar regions. The lower two-thirds of the lungs are mainly affected. The perihilar infiltration often has a butterfly or batwing pattern.

Differential diagnosis of the roentgenographic findings includes: pulmonary edema; sarcoidosis; pneumocystis Carinii pneumonia; pneumoconiosis, particularly berylliosis, asbestosis and nephaline lung; allergic disorders including periarteritis nodosa and Löffler's syndrome; and lymphangitic spread of carcinoma. Cardiac enlargement, pleural effusion, significant hilar lymphadenopathy, cavitation and calcification are not features of uncomplicated alveolar proteinosis.

Corticosteroids have no consistent beneficial effect on the disease process and are contraindicated because they predispose to secondary pulmonary infection, particularly with fungi. Cryptococcosis, nocardiosis and mucormycosis have occurred during steroid therapy in this disease, with subsequent fatal systemic fungal infection.

Aerosol therapy using streptokinase, streptodornase or trypsin have been reported to produce symptomatic improvement. Endobronchial infusions of heparin and saline and of crystalline trypsin have been effective in certain cases. Many feel that endobronchial infusions offer more effective results than the aerosols. It appears that therapeutic efforts should be directed towards softening or liquefying the alveolar proteinaceous material so that it may be expectorated.

Pulmonary insufficiency occurs late in the disease with cyanosis and clubbing of the fingers.

Spontaneous remissions and possible cures have been reported. However, in view of the apparent tendency for this disease to undergo remissions and exacerbations over a period of years, the prognosis must be guarded as far as recovery is concerned.—
Alan G. Greene, M.D.

HAYNIE, THOMAS P., HENDRICK, CHARLES K., and Schreiber, Melvyn H. Diagnosis of pulmonary embolism and infarction by photoscanning. J. Nuclear Med., Sept., 1965,

6, 613-631. (From: Section of Nuclear Medicine, University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, and Departments of Internal Medicine and Radiology, and Nuclear Medicine Service, University of Texas Medical Center, Galveston, Texas.)

The authors summarized their experience in the first 20 patients who had lung scans in their institution performed with I<sup>131</sup> tagged macroaggregated human serum albumin.

These 20 patients were divided into 3 groups on the basis of all available information except lung scan. Group I consisted of 9 patients who had definite or probable pulmonary embolic disease; Group II of 4 patients who had possible pulmonary embolic disease; and Group III of 7 patients who had a history suggestive of pulmonary embolism and laboratory tests indicating other diagnoses.

Abnormal lung scans, showing "cold" areas were found in all but I patient in Group I. The chest roentgenogram was abnormal in 7 out of 8 patients examined and 5 patients in this group had abnormal angiocardiograms.

In Group II, 2 out of 4 patients had abnormal scans. One patient had pulmonary hypertension which was thought to be the result of multiple small emboli, but the lung scan was normal. The second patient with normal scan had clinical signs of pulmonary infarction but no roentgenographic findings.

Group III comprised a variety of pulmonary disorders, except for I normal volunteer. The lung scan was abnormal in 5. These abnormalities on the scan were due to other pathology such as pericardial effusion, subdiaphragmatic abscess, neoplasm, or pulmonary emphysema.

The lung scan is easy to perform and offers a simple method for initial diagnosis of pulmonary embolism and infarction as well as for follow-up study. Although this method shows a good correlation with the clinical diagnosis of pulmonary embolism and infarction, it should not be relied upon as the only procedure. It is felt that scan is of diagnostic value especially when used in conjunction with roentgenologic study of the chest.—Abbas M. Rejali, M.D.

#### ABDOMEN

LAUDAN, J. C. H., and GREIO, J. H. Celiac axis occlusion: two cases diagnosed angiographically. J. Canad. A. Radiologists, Sept., 1965, 16, 190–194. (From: Shaughnessy Hospital, Vancouver, British Columbia, Canada.)

The authors report 2 cases of arteriosclerotic occlusion of the celiac axis, diagnosed angiographically.

In the case of a 55 year old man there was occlusion of both the celiac axis and the inferior mesenteric arteries, with collateral circulation via the pancreaticoduodenal arcade and the central anastomotic

artery of the colon, respectively, from the superior mesenteric artery. He suffered from intestinal angina.

The second case was an 83 year old man who had no gastrointestinal symptoms. An angiogram revealed that he suffered from occlusion of the celiac axis with collateral circulation from the superior mesenteric artery via the less usual anastomotic artery of Bühler.

The authors feel that abdominal angiography in the study of intestinal angina can be of vital value to the vascular surgeon.—Arthur E. Childe, M.D.

REUTER, STEWART R., and OLIN, TORD. Stenosis of the celiac artery. *Radiology*, Oct., 1965, 85, 617–627. (From: Roentgendiagnostic Department, University Hospital, Lund, Sweden.)

The celiac axis is commonly involved by generalized atherosclerosis but stenosis or occlusion of this vessel is seldom described as a cause for abdominal angina. The syndrome of intestinal vascular insufficiency may be due to inadequate flow through the superior mesenteric artery, but it can be produced by combined celiac and inferior mesenteric artery stenosis in the presence of a normal superior mesenteric artery.

To clarify the clincal significance of stenosis or occlusion of the celiac artery the authors have studied the angiographic and clinical findings in 17 cases of celiac artery disease. Four were examined specifically because of suspected disease in the aorta or its abdominal branches, while the remaining 13 cases represent celiac vascular disease discovered among the 720 selective celiac and superior mesenteric arteriographic studies performed at the University of Lund since 1959.

The observed stenosis of the celiac artery always began at the orifice and usually it was short. The flow patterns observed at selective arteriography depended on the degree of stenosis and the vascular anatomy. The collateral channels most constantly developed to supply a stenosed celiac artery were those over the head of the pancreas, representing enlarged pancreaticoduodenal arcades and the gastroduodenal artery. In the absence of hepatic tumors, vascular anomalies, or cirrhosis, the degree of development of these collaterals correlated with the degree of celiac artery stenosis.

The clinical evaluation of this group of 17 patients disclosed that in 12 patients, no symptoms could be related to intestinal vascular insufficiency. One patient had mild celiac stenosis which probably did not produce the noted abdominal pain. Therefore, in 4 patients only, 2 with celiac and inferior mesenteric stenosis and 2 with celiac stenosis and cirrhosis, the possibility exists that the abdominal pain was related to the celiac stenosis.

It is the authors' opinion that celiac stenosis alone causes no symptoms. However, when other diseases

exist, which either increase the demand for or further compromise intestinal blood flow, the symptoms of intestinal vascular insufficiency may appear.—Edward B. Best, M.D.

RABINOV, KEITH R., and SIMON, MORRIS. Peroral cannulation of the ampulla of Vater for direct cholangiography and pancreatography: preliminary report of a new method. Radiology, Oct., 1965, 85, 693-697. (From: Department of Radiology, Harvard University Medical School, and Department of Radiology, Beth Israel Hospital, Boston, Mass.)

Because existing radiologic methods may fail to demonstrate the biliary ducts in jaundiced patients and do not at all opacify the pancreatic ducts, it was decided to test the feasibility of cannulating the ampulla of Vater by intubation through the mouth, using television fluoroscopic monitoring.

A prototype combination intubation-cannulation instrument was constructed and this instrument, along with the biologic and technical factors related to the procedure, is described. The anatomic variations and technical difficulties demand improvements in the application of this approach and particularly indicate the need for direct visualization. It is pointed out that this approach, to date, has been limited to 8 patients in whom standard methods failed to provide a diagnosis. A preliminary barium meal examination is done for gross anatomic relationships and evidence of upper gastrointestinal tract disease that might contraindicate the procedure. Cannulation of the ampulla, injection of the biliary and pancreatic ducts with renografin, and diagnosis were accomplished twice in the same patient, but were unsuccessful in each of the other 7 cases. However, the procedure is tolerated and excessive discomfort has not been noted. Most patients do have some diarrhea following the examination, apparently due to the large quantity of the contrast medium passing through the gastrointestinal tract, but there has not been a hemorrhage or perforation. Post-examination serum amylase was not elevated and in selected patients it is assumed that injection of the pancreatic ducts would be tolerated. Repeat barium meal examination following both successful and unsuccessful attempts to cannulate the ampulla failed to reveal any evidence of compromising injury. The examining instrument was passed in I patient with esophageal varices, in 2 with duodenal diverticula, and in 2 with active duodenal disease. Contraindications to the cannulation would include gastric resection, severe stenosis or obstruction of the upper gastrointestinal tract, and possibly pharyngeal diverticula.

The ultimate frequency with which the biliary or pancreatic ducts can be cannulated is not known and the success of this method will depend upon improvement and adaptability of the instrument. That the method is technically feasible has been demonstrated. —John Bond, M.D.

Svoboda, M., and Fiala, J. Der Einfluss von Bilivistan auf die osmotische Resistenz und Hämolyse roter Blutkörperchen. (The influence of Bilivistan on the osmotic resistance and hemolysis of red blood cells.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, Oct., 1965, 103, 491–493. (Address: Unemocnice 1, Praha 2, Czechoslovakia.)

Blood from 20 healthy donors was used for 200 in vitro tests to assess the osmotic resistance of the erythrocytes and the amount of hemoglobin set free by diluting blood with bilivistan (Schering) 1:7, 1:15, 1:100 and 1:200.

Bilivistan had less effect and a more uniform effect on the red blood cells than did biligrafin; therefore, bilivistan appears more desirable from the hematologic viewpoint.—Henry G. Moehring, M.D.

#### GYNECOLOGY AND OBSTETRICS

VICKERS, ANTHONY A. Placentography simplified. *Clin. Radiol.*, Oct., 1965, 16, 351–362. (From: Radiological Department, Ronkswood Hospital, Worcester, England.)

The author reviews the results of a simplified approach to direct placentography in 259 cases over a 7 year period from 1956 to 1962, with emphasis on the sources of error. Direct soft tissue placentography was placed on a secure foundation by Reid (1949) who gave a convincing exposition of the components of the soft tissue "placental shadow," which included uterine wall, anything from no placenta to its maximum thickness, and a variable depth of liquor.

Simplified placentography is restricted to assessment of the relationship of the fetal presenting part to the pelvic brim. It does not eliminate false positive diagnoses of placenta previa, but this complication of pregnancy can be excluded with reasonable reliability.

Placenta previa is classified by the author as follows:

Grade 1— The placenta reaches down to the lower segment

Grade 2— The placenta reaches the edge of the internal os

Grade 3— The placenta reaches across to the far edge of undilated internal os

Grade 4— The placenta reaches across to the far edge of the internal os, even at full dilatation

The routine examination includes: (a) a lateral erect roentgenogram of the pelvis. If the presenting part is displaced forward from the promontory, then (b) a lateral erect roentgenogram, but with the pelvic

brim horizontal, using a horizontal projection of radiation is made.

Of the 259 cases reviewed, there were 5 patients with false negative results (missed placenta previa). In 42 cases, out of 87 positive results, there were false positive placentograms. Of the 5 false negatives listed by the author, 2 were roentgenographic errors of judgement. The remaining 3 showed minor displacements, even though one of these was a Grade 3 placenta previa. (The space between the breech and sacrum appeared to be occupied by the rectum.) Among the false positives some classed as errors were cases where the diagnosis was not proved or not confirmed.

There will always remain a proportion of placentas in which there is room for diversity of opinion as to whether true placenta previa is present. The important fact is that while a Grade I anterior placenta previa is usually considered to be of little clinical significance, a Grade I posterior placenta previa is thought to be responsible for a significant impairment of placental circulation, as its edge becomes cut off by pressure of the presenting part against the lumbosacral promontory.—Samuel G Henderson, M.D.

Hanafee, William, and Bashore, Richard. Carbon dioxide and horizontal fluoroscopy in intrauterine fetal transfusions. *Radiology*, Sept., 1965, 85, 481–484. (From: University of California, Los Angeles, Calif.)

Anemia is the major cause of death of the erythroblastotic fetus prior to viability. Correction of the anemia until viability is therefore, an important step in salvaging these fetuses. It has been shown that erythrocytes are absorbed intact from the fetal peritoneal cavity and, on this basis, a recent method of attempting to correct the anemia is by transfusion of packed red cells into the peritoneal cavity of the intrauterine fetus via a maternal transabdominal and transuterine approach.

The major problem lies in accurately placing a catheter into the fetal peritoneal cavity so that the packed red blood cells will be absorbed by the fetus. A widely used technique has been to inject 20 cc. of a solution of radiopaque material, such as urografin, into the amniotic cavity, then allow time (about 5 hours) for the fetus to swallow sufficient amount of the urografin-containing amniotic fluid to opacify the bowel. Markers are placed on the skin of the maternal abdomen and anteroposterior and lateral roentgenograms of the abdomen are taken. Using these roentgenograms, it is possible to arrive at an approximate angle for insertion of the needle into the fetal peritoneal cavity. The needle is first inserted into the amniotic cavity then the stylet is removed and a syringe containing sterile saline is attached. As the needle is further advanced, the saline is slowly injected until a resistance to the flow of saline is met at the fetal abdominal wall, followed by a free flow again once the peritoneal cavity is reached. A catheter is inserted through the needle bore into the cavity and the needle removed. To be sure of proper catheter positioning, methylglucamine diatrizoate (3 cc.) is injected and another roentgenogram taken, which will reveal bowel loop shadows if the catheter is properly placed.

The purpose of this paper is to describe a more rapid and possibly safer method of placing the catheter, utilizing horizontal fluoroscopy with image intensification for guidance of the needle, and carbon dioxide insufflation as a double check for proper catheter placement. Initially, anteroposterior and translateral roentgenograms of the maternal abdomen in the supine position are taken to ascertain fetal position with relation to the maternal spine and iliac crest. Then, again with the mother in a supine position, under horizontal fluoroscopic guidance a needle is inserted through the anterior maternal structures, through the anterior or lateral fetal abdominal wall into the peritoneal cavity, leaving the needle stylet in place until the cavity is reached. After this the stylet is removed and 2-5 cc. carbon dioxide is injected into the cavity through a syringe attached to the needle. If the needle is in the fetal peritoneal cavity the gas will be seen in the fetal abdomen on fluoroscopy. The catheter is then slipped into place and the needle withdrawn, after which the packed red blood cells are infused slowly over a 30-60 minute period.

The advantages of this method over the older one are that it saves time, eliminates considerable guesswork, and because there are no radiopaque solutions used, obviates toxic reactions to these materials.

The article has a clear photograph of the materials used and of a roentgenogram showing CO<sub>2</sub> in the amniotic sac and fetal peritoneal cavity.—Victor B. Brasseur, M.D.

#### GENITOURINARY SYSTEM

Servadio, C. A modified technique for intravenous pyelography. *Brit. J. Urol.*, Aug., 1965, 37, 385–389. (From: Department of Urology, Hadassah University Hospital, Jerusalem, Israel.)

A modification of the standard pyelographic technique is presented. The patient is instructed to remain in a fasting state for a 12 hour period prior to the examination. A laxative is given the evening before. The essential difference from other urographic techniques lies in the fact that abdominal compression is initiated for up to 12 minutes prior to the injection of the contrast medium. With the compression maintained, films are exposed at 4, 12, and 20 minutes after the injection, also at later intervals if required. At least 1 film is exposed following release of the compression to exclude any possibility of a m'sleading artefact.

The author claims that by initiating abdominal

compression prior to the injection of the contrast material, the renal pelvic pressure is given sufficient time to build up to an adequate level before the contrast medium reaches the collecting system. This allows for an even greater concentration of the contrast medium than can be achieved by applying abdominal compression after the initial injection. Even though compression in itself introduces undesirable artefactual changes, the clearer delineation of the pyelocalyceal system is an advantage that definitely outweighs the inherent defects of the method.

The technique is simple, safe, and only causes minimal discomfort to the patient. The only contraindications to its use are those associated with conventional intravenous pyelography.

The author presents and discusses 3 cases that tend to support his contention that this modified pyelographic technique is far superior to the ordinary intravenous study.—Kenneth M. Nowicki, M.D.

Dee, P. M. Generalised bullous oedema of the bladder. *Clin. Radiol.*, Oct., 1965, 16, 328–329. (From: Department of Radiology, Royal Victoria Infirmary, Newcastle upon Tyne, England.)

Generalized bullous edema appears to be secondary to pelvic lymphatic stasis at a distance from the bladder, as contrasted with the more localized type. The latter may occur in association with direct infiltration of the bladder by a primary carcinoma. The lymphatic obstruction associated with generalized bullous edema may be the result of infiltration of the pelvic lymphatic system by neoplastic cells from a carcinoma of the uterine body or cervix, or it may be the result of radical excision of pelvic lymph nodes.

Bullous edema produces an abnormal and easily recognized roentgenographic pattern. The bladder presents an irregularly scalloped outline, with a large number of rounded filling defects giving a "soap bubble" appearance.—Samuel G. Henderson, M.D.

SHAWDON, HARRY H., DOYLE, FRANK H., and SHACKMAN, RALPH. Double contrast cystography applied to the diagnosis of tumours in bladder diverticula. *Brit. J. Urol.*, Oct., 1965, 37, 536–544. (From: Departments of Radiodiagnosis and Surgery, Postgraduate Medical School of London, Hammersmith Hospital, London, England.)

Double contrast cystography as described by F. H. Doyle in the *British Journal of Radiology*, 1961 and 1963, has proven valuable in distinguishing tumors within bladder diverticula.

Steripaque, 150 ml., is introduced into the bladder through a catheter under fluoroscopic control. Most of the contrast medium is then removed and 150 ml. of carbon dioxide is injected. Posteroanterior roent-genograms of the bladder are made with the patient in erect, Trendelenburg, and both lateral decubitus

positions, supplemented sometimes by roentgenograms in oblique projections.

The authors report 4 cases in which tumors arose within large bladder diverticula, and the diagnosis was made preoperatively primarily by the double contrast cystogram.

Very small lesions can be found if the procedure is carefully performed, the method being quite as valuable as double contrast colon studies.—Arch H. Hall, M.D.

NOGRADY, M. B., and DUNBAR, J. S. The value of excretory micturition cysto-urethrography (EMCU) in the pediatric age group. J. Canad. A. Radiologists, Sept., 1965, 16, 181–189. (From: Department of Radiology, The Montreal Children's Hospital, Montreal, Quebec, Canada.)

The authors feel that radiologic examination of the lower urinary tract by the excretory method permits a more thorough and physiologic evaluation of the entire urinary tract than any other single diagnostic procedure.

They describe their technique in detail. The patients are not dehydrated but renografin 60 is used in relatively high dosage up to a maximum of 25 ml. for relatively young infants and up to 50 ml. in older children. When infants are examined they are strapped to a special platform immediately after the 6 minute film has been exposed and placed in a lateral position. Then, depending on the problem, either a single overtable roentgenogram is made or cinefluorography for 5½ seconds duration is carried out. The exposures are automatically triggered by the urinary stream which flows through a "perineal unit," and thereby closes a circuit which activates the exposure mechanism. In older patients who will cooperate, the lower urinary tract study is done in a nearly upright position with the pelvis rotated slightly away from the true lateral projection. When voiding occurs, cinefluorography is initiated, interrupted once or twice for exposure of spot films. The cine is only allowed to run for a brief time after voiding but a short strip of film is made after this to scan the bladder area and each kidney.

This method of examination has the advantage of avoiding the physical and psychic trauma of catheterization and the possibility of introducing injection from below. It is also felt that the findings obtained from excretory studies are more physiologic and more reliable than those by any retrograde method. Visualization of the lower urinary tract is good in the first 6 months of life but in the older child and adult it is less satisfactory. Its use is limited in the age group from 6 months to  $2\frac{1}{2}$  years due to lack of necessary patient cooperation. The radiographic room may be occupied for a longer period than with retrograde methods and the amount of radiation delivered to the gonads may be greater. However, in-

creasing experience should reduce this latter disadvantage. It is also admitted that slight vesico-ure-teral reflux is more difficult to recognize by the excretory method.

The authors stress the importance of careful collimation of the roentgen-ray beam and limitation of cine runs to the moments of voiding and immediate post-voiding periods.—Arthur E. Childe, M.D.

Jarzylo, S. V., Challis, T. W., and Bruce, A. W. Urachal abnormalities. J. Canad. A. Radiologists, Sept., 1965, 16, 175–180. (From: The Kingston General Hospital, Kingston, Ontario, Canada.)

The urachus is a tubular connection between the urinary bladder and the umbilicus in the pro-peritoneal tissues. The various abnormalities of the urachus which occur may be classified into four groups: (1) complete, the urachus being patent throughout its course; (2) blind internal, giving rise to a vesicourachal diverticulum; (3) blind external, forming a urachal sinus; and (4) urachal cyst.

The authors feel that abnormalities of the urachus may not be as rare as has been previously suggested. They have found 4 in 5,606 consecutive intravenous pyelograms: 3 in male infants and children and 1 in a female, aged 38 years.

An important complication of a patent urachus is infection spreading not only to the bladder but also to the umbilicus. In the case of a 6 year old boy, they suspect that urachal diverticulum was the site of chronic infection which caused cystitis and the formation of a large bladder calculus. However, some urachal abnormalities are discovered incidentally and remain asymptomatic throughout life.—Arthur E. Childe, M.D.

MAGED, ALY. Urethral diverticula in males (with a report of eight cases). Brit. J. Urol., Oct., 1965, 37, 560–568. (From: Department of Urology, Faculty of Medicine, Ein Shams University, Cairo, U.A.R.)

While urethral diverticula are not uncommon in females, they are quite rare in males.

The author adds 8 cases to the literature bringing the total number of male urethral diverticula reported to slightly over 200.

Congenital diverticula are infrequent.

The more common acquired types are caused by abscesses, trauma from instrumentation or external injury, pressure from urethral calculus, neurogenic dysfunction, and bilharziasis—the latter being common in Egypt. In general, these diverticula do not give rise to symptoms and may reach considerable size before the patient seeks medical advice. Involuntary dribbling of urine and a palpable penile or scrotal mass are then noted.

The diagnosis is easily confirmed by cystourethrography.—Arch H. Hall, M.D.

WRIGHT, F. W. Cavography in the assessment of renal tumors. *Brit. J. Urol.*, Aug., 1965, 37, 380–384. (From: Department of Radiology, United Oxford Hospitals, Oxford, England.)

Carcinoma of the kidney frequently grows through the renal veins into the inferior vena cava.

The author feels that cavography is important in the assessment of renal tumors from the diagnostic point of view because an anterior approach may be necessary to resect the tumor. Nephrectomy is normally carried out through a lateral incision. On the right side, it is quite easy to examine the renal vein and inferior vena cava and to remove the renal vein and part of the vena cava if necessary. However, on the left side the renal vein is much longer, passing to the right in front of the aorta. It is possible to examine and resect only its more lateral portion through a lateral incision. For this reason, if the renal vein is affected, an anterior approach would be necessary for adequate surgical incision. Extension of the tumor into the renal vein is seen relatively commonly when a surgical specimen is examined. Cavography will determine if the tumor has spread into the cava. The renal veins themselves do not usually fill.

Cavography was performed by passing catheters up both femoral veins into the common iliac veins by the Seldinger technique. Both catheters are joined together and 30 to 40 ml. of contrast material is injected by hand pressure using a lever in about 2 seconds. Anteroposterior and right posterior oblique projections were employed.

Three cases of left sided renal tumors are reported with extension into and involvement of the inferior vena cava.—Alan G. Greene, M.D.

GILLOT, C., STUHL, L., and ECOIFFIER, J., with the collaboration of AARON, C., CHASSAING, P., and MOUÏEL, J. (Paris, France.) La phlébographie rénale occlusive: technique et résultats normaux. (Occlusive renal phlebography: technique and normal results.) Presse méd., Sept. 23, 1965, 73, 2215–2220.

A method is described for studying the renal veins. A catheter is inserted through the saphenous vein into the inferior vena cava and balloons are distended above and below the entrance of the renal veins. A quantity of 70 ml. of contrast medium is injected under pressure of 1.6 kg. This gives a very good demonstration of the venous system of both kidneys, the left suprarenal vein and many of the veins connecting with these same veins. Heparin is used during and after the procedure to prevent thrombosis.

The normal anatomy is described and 10 roent-genographic illustrations show the venous systems very well. A future report will describe pathologic changes.—Charles M. Nice, Jr., M.D., Ph.D.

#### NERVOUS SYSTEM

NEHLIL, J. Multinévrite à rechutes associée à des manifestations osseuses cutanées et cardiaques: affection apparentée à la maladie de Refsum ou maladie autonome? (Recurrent multineuritis associated with osseous, cutaneous, and cardiac manifestations: Refsum's disease or new disease?). Presse méd., Sept. 11, 1965, 73, 2081–2084. (From: Hôpital Dispensaire-Ecole Henri-Dunant, Paris, and Centre hospitalier d'Argenteuil, Argenteuil, France.)

Refsum's disease is a genetic affection characterized by association of a peripheral neuritis resembling the hypertrophic neuritis of Dejerine-Sottas, retinitis pigmentosa, and a cerebellar syndrome. It may be associated with ichthyosis.

A case is reported of a 59 year old female who had a relapsing multineuritis affecting the cranial nerves and later the peripheral nerves. In addition there were deformities of the elbows, bilateral club foot with areas of bone destruction, and changes in the electrocardiogram, slowing of eye reflexes, hypoacusis, diabetes, and cutaneous ichthyosis. This patient had several of the aspects of Refsum's disease but varied in that there were cranial nerves involved, bone abnormalities, and alopecia which are usually lacking in Refsum's disease. On the other hand, the retinal involvement usually denoted in Refsum's disease was not present.—Charles M. Nice, Jr., M.D., Ph.D.

#### BLOOD AND LYMPH SYSTEM

Davis, Carl B., Jr., Fell, Egbert H., and Taylor, C. Bruce. Postoperative aneurysm following surgery for coarctation of aorta. Surg., Gynec. & Obst., Nov., 1965, 121, 1043–1048. (From: Department of Surgery, Presbyterian-St. Luke's Hospital, Chicago, Department of Surgery, University of Illinois College of Medicine, Department of Pathology, Evanston Hospital, Evanston, and Department of Pathology, Northwestern University Medical School, Chicago, Ill.)

The authors report 3 cases of aneurysm occurring at the site of anastomosis following resection of coarctation of the thoracic aorta. All aneurysms developed within 1 year following the operation. Reoperation was attempted in 2 of the 3 cases with insertion of synthetic grafts. One of these patients is alive and well. The unoperated case died as a result of the rupture of a false aneurysm at the site of the anastomosis. A review of similar cases from the literature revealed some cases attributed to operative bacterial endarteritis. A routinely found morphologic defect was the loss of continuity of elastic fibers of the media at the suture line.

The authors recommend close postoperative followup to recognize these aneurysms and early surgical treatment, because of the possibility of continued expansion and risk of fatal rupture of the aneurysm.

Several reproductions of roentgenograms are presented to demonstrate the appearance of the post-operative aneurysms.—Donald S. Linton, Jr., M.D.

Bobbio, P., Peracchia, G., and Schippisi, G. Gaononi. Le modificazioni indotte dalla radioterapia sul sistema linfatico ascellare in presenza di metastasi linfonodali e dopo svuotamento chirurgico del cavo per cancro mammario. (Modifications induced by radiation therapy on the axillary lymphatic system in the presence of metastases to the lymph nodes and after surgical evacuation of the axillary cavity for mammary cancer.)

Ann. radiol. diag., 1965, 38, 1–65. (From: Istituto di Patologia Speciale Chirurgica e Propedeutica Clinica dell'Università di Parma, and Istituto di Radiologia dell'Università di Parma, Italy.)

Lymphadenography was carried out in patients with cancer of the breast who were treated either by irradiation alone or associated with simple or radical mastectomy.

In patients treated by irradiation alone or by simple mastectomy and irradiation, the lymphographic studies were made before cobalt 60 teletherapy, and periodic roentgenograms of the axillary region were made for 6 to 12 months after the end of treatment. In patients who had radical mastectomy, lymphadenography was performed 30 to 45 days after surgery and before radiation therapy. A control roentgenogram of the axilla was made a few months after the treatment was completed.

In the first group of patients, the lymphadenographic findings were characterized by a reduction in size of the enlarged lymph nodes with diminished permeability to the flow of the contrast medium; disappearance of the short collateral lymphatics between lymph nodes; and the visualization of a cutaneous collateral lymphatic circulation, mostly in the medial aspect of the arm. In those cases which developed localized fibrosis, the damage to the lymphatic system by the radiation therapy was more severe and the very poor permeability resulted in an obvious edema of the arm.

In the group of patients treated by radical mastectomy and irradiation with doses up to 2,000 r, there was only a functional damage and no changes in the gross appearance of the lymph nodes. With doses of more than 3,000 r, the lymphatics of the axilla were severely damaged and not infrequently there was blockage to the the lymphatic flow. This effect is due not only to the direct action on the lymph nodes but also to a severe process of fibrosis in the tissue of the

axilla already damaged by the surgical intervention. Ultimately, the lymphatic drainage takes place through the satellite lymphatics of the axillary vein. In patients treated with higher doses the changes were essentially the same. In cases which developed marked edema of the arm, the changes in the lymph nodes and pathways were secondary to severe postradiation fibrosis.

Concluding, the authors state that the changes in the lymphatic pathways of the axilla depended more on the radicality of the surgical intervention than on the amount of radiation received by the patient.—

A. F. Govoni, M.D.

Beltz, L., and Thurn, P. Lymphography in retroperitoneal lymphatic blockage due to malignant tumor. *German Med. Monthly*, Aug., 1965, 10, 323-326. (From: Department of Radiology and Radiotherapy of the Municipal Hospitals, Aachen, Germany.)

Primary neoplasms of the lymphatic system rarely cause obstruction of the lymphatic flow, while filling defects in the lymphatic channels with obstruction to lymph flow are common in cancer metastases. Cancers of the uterus, vagina and bladder usually spread to the retroperitoneal lymphatic system, while those involving the testicle, ovary, kidney, etc., spread to the para-aortic lymph nodes.

In case of metastases to the retroperitoneal lymphatic channels, collateral circulation may develop in several fashions: (1) within the retroperitoneal lymphatic system: (2) via the lymphatic systems of neighboring organs; and (3) in lymphatic venous anastomosis.

Lymphography can demonstrate lymphatic collateral pathways when obstruction has been produced by metastatic retroperitoneal cancer. Since there is a close relationship between venous and lymphatic systems, it is necessary to exclude venous obstruction when studying lymphedema secondary to retroperitoneal lymph node metastases or lymphedema of the arm secondary to surgical and radiation treatment of breast carcinoma.—Richard E. Kinzer, M.D.

MICELI, R., CORINALDESI, A., and RIMONDI, C. Modificazioni dei quadri linfografici iliaci e lombo-aortici in seguito ad irradiazione. (Modifications of the iliac and lumbo-aortic lymphographic patterns, following irradiation.) Radiol. med., June, 1965, 51, 629–650. (Address: Dott. Prof. Roberto Miceli, Via Giuseppe Ruggi, 5, Bologna, Italy.)

Lymphadenography was performed in 30 patients who later were treated by radiation therapy for leukemia, lymphosarcoma, reticulum cell sarcoma, malignant lymphogranuloma, metastases from me

lanoblastoma of the lower limbs, carcinoma of the testis, and carcinoma of the uterus.

The lymphographic study was done immediately before the treatment and periodic roentgenograms of the opacified lymphatics were made during, immediately after, and at intervals of several months from the end of the radiation therapy; the lymphographic patterns were then compared and evaluated.

Analyzed were the changes in size, shape and location of the lymphatics and lymph nodes, distribution of the contrast material and its spontaneous elimination

Comparing periodic lymphadenograms made in subjects with a normal iliac and lumbo-aortic lymphatic system with similar lymphadenograms made in patients treated by radiation therapy but also having normal lymphatics, the following lymphographic patterns were noted: (1) marked reduction in size and degree of opacification of the lymph nodes, with a relative increase in size of the smaller lymph nodes; (2) an earlier appearance of the granular pattern in the opacified lymph nodes; and (3) faster disappearance of the contrast medium. These findings were noted from 2 to 3 months from the end of the radiation therapy and in those patients who received doses above 3,000-4,000 r to the lymph nodes.

The analysis of the neoplastic lymphadenographic patterns following irradiation showed a different reaction in the lymph nodes whether involved by a mesenchymal neoplasm or by metastases from epithelial tumors. In leukemia and lymphosarcoma the periodic lymphograms demonstrated a rapid regression of the enlarged lymph nodes with homogeneous and increased density and early normalization of the lymphographic pattern. In malignant lymphogranuloma the regression of the enlarged lymph nodes was slower and no evidence of normalization of the lymphograms was noted. Lumbo-aortic lymph nodes involved by metastases from seminoma of the testis showed a constant regression with normalization of the lymphogram. Not so pronounced were the changes observed in the lymphographic patterns of patients with metastases from cancer of the cervix uteri. There were no essential changes in the iliac lymph nodes of the patients with metastases from melanoma involving both lower limbs.—1. F. Govoni, M.D.

DE DOMINICIS, R., BUFALINI, G. NORI, and RAGAGLINI, G. La nostra esperienza in tema di linfografia. (Our experience in the field of lymphadenography.) *Radiol. med.*, June, 1965, 51, 587–629. (Address: Dott. Prof. Giorgio Ragaglini, Piazza Matteotti, 32, Pietrasanta [Lucca], Italy.)

The authors performed intralymphatic injections of ultrafluid oil contrast material in 155 patients.

In 122 cases the contrast medium was injected

into the lymphatics of both feet, in 26 cases into one foot only, and in 7 patients the contrast material was injected through the lymphatics of the funicular process. In 3 cases the examination was repeated twice, from 15 days to a year after the first lymphadenography—following surgical intervention or radiation therapy of the abdomen.

Pulmonary oil embolism occurred in 2 cases. In 1 the clinical recovery was complete in a few days. The other case did not recover and the cause of death was thought to be reaction to the contrast medium.

The procedure was unsuccessful in only 5 per cent of the patients.

The case material discussed in this analysis comprised: 19 cases with Hodgkin's disease; 13 cases with reticulum cell sarcoma or Brill-Symmers disease; 56 cases with carcinoma of the cervix uteri; 18 cases with carcinoma of the ovary and body of the uterus; 14 cases with tumors of the testicles; 5 cases with carcinoma of the bladder; and 4 cases with carcinoma of the prostate.

Several cases are reported and the lymphographic findings are discussed in detail.

In concluding, the authors confirm the proven importance and value of lymphadenography.—A. F. Govoni, M.D.

MARTINS DA ROCHA, R., DE SOUZA, AYRES, ELIAS DA COSTA, C., and LEITAO, M. (Lisbon, Portugal.) Quelques aspects lymphographiques dans la pathologie tropicale. (Lymphography in tropical diseases.) J. belge de radiol., 1965, 48, 275-294.

The authors mention that shortly after Egas Moniz published his work on cerebral angiography, three other Portuguese investigators reported, on February 5, 1931, to the Société d'Anatomie à Paris, their work on opacification of the lymphatics in the living subject. The first work was done on dogs. Subsequently, in August of the same year, they reported their work on human beings.

The authors have performed lymphography on patients with different tropical diseases, but in this presentation, they limit their report to Microfilaria bancrofti.

The technique of Kinmonth is used with initial injection of a coloring material into the subcutaneous tissue for visualization of the lymphatics, followed by the injection of an opaque contrast medium into the lymphatic vessels. Their preference is a lipo-soluble or fat soluble medium rather than a water soluble contrast medium. Ten cc. of extra-fluid lipiodol may be injected simultaneously into both lower extremities.

The authors vary the technique of the examination to meet the needs of each individual. The first roent-genogram is made after the injection of 0.5 cc. to confirm the position of the needle in the lymphatic structure. The second roentgenogram is made after 3 cc. has been injected for visualization of the leg. A

roentgenogram of the knee is made after 7 cc. and of the thigh and groin, after 10 cc. has been injected. Delayed roentgenograms are made at or after 24 hours.

The incubation period of microfilaria varies between 3 and 18 months. In 50 per cent of infected cases there may be no clinical symptoms, and the disease remains in a subclinical phase. However, lymphographic studies will reveal pathologic alterations of the lymphatic system, evidenced by enlarged lymph nodes and vessels, with changes in the caliber and appearance of the latter.

In the clinical phase lymphangitis is the predominant lesion, presenting obstructive symptoms, such as adeno-lymphecele, lymphedema, and elephantiasis. The adult worm lodges in the lymphatic trunk and sets up a toxic-allergic inflammatory process in the vessel wall. At the same time granulation tissue and eventually fibrosis occur with eventual obliteration of the lymph vessels.

The degree of obliteration of the lymphatic vessels, the location and the number of vessels involved determine the degree and type of symptoms.

The authors include 19 figures and reproductions of roentgenograms of interesting cases, presenting various stages and degrees of involvement of the lymph vessels and nodes by the parasite.—William H. Shehadi, M.D.

#### GENERAL

Murphy, Kevin J., and McPhee, Ian. (Brisbane, Australia.) Tears of major tendons in chronic acidosis with elastosis. J. Bone & Joint Surg., Sept., 1965, 47-A, 1253-1258.

Chronic acidosis has been found to be associated with connective tissue elastosis in the dermis, lungs, aorta, cartilage and bone. A similar change in the tendons was present in a 39 year old male with chronic lead nephropathy. He tripped, fell forward and ruptured the right quadriceps tendon, the left patellar tendon and the right triceps tendon.

Roentgenograms showed extensive changes of secondary hyperparathyroidism and widespread arterial calcification. Quadriceps tendon biopsy showed many fibers taking the elastic tissue stain.—
Martha Mottram, M.D.

GRIGG, E. R. N. The new history of radiology. *Radiologic Technology*, 1965, 36, 229–257. (From: The Department of Radiology, Cook County Hospital, Chicago 12, Illinois.)

The author is a well known writer and authority on history of radiology. In a masterly fashion in this paper he briefly encompasses the history of radiology since its birth to the present day.

Vividly, authoritatively, and often with a refreshing combination of philosophy and witticism, he relates, step by step, the stages of development and

evolution of radiology as it grew to its present day status. Each stage moves smoothly into the next, intertwining one with the other.

In a series of elaborate and carefully worked out tables he brings out the advances in technique, with concomitant progress in diagnosis and therapy, development in the manufacture of X-ray equipment, the appearance of individual companies, the intricate mergers which developed, and the resultant advance in equipment. Included, also, are the stages of development in the use of the roentgen rays in diagnosis and therapy, radium and radioactive isotopes. There is a brief reference to the birth and development of the leading national radiological societies and several regional or local societies.

Books of rare historic significance are listed (and they are rare books, some of which, only after ardent search over the years, this reviewer was able to acquire for his own library), many of which are a "must" for a student of the history of radiology.

Three major eras in the history of radiology are identified, The Era of Roentgen Pioneers, The Golden Age of Radiology, and The Atomic Phase.

The important role of the X-ray technician (radiologic technologist) and of the physicist, as part of the "radiologic team," are rightly stressed.

Photographs of several of the pioneers and of several historic events add to the value of the text.

This article is a natural prelude to the author's forthcoming book, *The Trail of the Invisible Light*, which with great skill, he has made "visible."— William H. Shehadi, M.D.

#### RADIATION THERAPY

Paterson, Ralston. Clinical trials in malignant disease: general principles. *Proc. Roy. Soc. Med.*, Aug., 1965, 58, 625-626. (From: Christie Hospital, Manchester, England.)

The genuine scientific comparison between different treatments or different aspects of treatment is the purpose of clinical trials when applied to human disease.

Requirement that no injustice be done to a patient on either side of the trial imposes definite difficulties when designing clinical trials with malignant disease.

The consequences in such a life or death situation include:

- The two defined policies must be equally acceptable.
- 2. The double-blind approach is not applicable. The physician must know what has been done; for in malignant disease the contrast is really between two intended policies, not between two treatments.

A clinical experiment is what is actually being performed in spite of the term clinical trial. The rigid discipline of good laboratory work is necessary for worthwhile results.—Ronald Schaupp, M.D.

HAYWARD, J. L. Planning and conducting cancer clinical trials. *Proc. Roy. Soc. Med.*, Aug., 1965, 58, 626–629. (From: Imperial Cancer Research Fund, London, and Guy's Hospital, London, England.)

Since credit for the pioneer work in clinical trials regarding cancer treatment has been ascribed to the British cancer researcher, the author feels it is important that these workers assume special responsibility to ensure that these trials are used appropriately.

Two points are tantamount to a good clinical trial:

- A method of comparison should be decided upon before the trial starts.
- 2. While in the planning stage, the method of comparison should not only be appropriate to the problem at hand, but it should be used in a reasonable manner and should stand at least a reasonable chance of revealing any difference there may be.

The difficulty of where to place the line between success and failure may be overcome by a rigid complex protocol as, the author cites, is found in the Cooperative Breast Cancer Group in the United States.

The Mean Clinical Values (MCV) (Walpole and Paterson, 1949) of lesions which are visible, palpable or demonstrable roentgenographically are measured before treatment. These are plotted on a scale and measured at regular intervals during and after treatment. This system, although not full-proof, does allow a linear comparison of many patients in a relatively uncomplicated manner. The ability of the patient to cope both physically and mentally with the condition of life that treatment has afforded her is also very important and often neglected.

The author mentions a questionnaire he routinely uses to assess this part of a patient's treatment.—
Ronald Schaupp, M.D.

McWhirter, R. Clinical trial undertaken in breast cancer in South-East Scotland. *Proc. Roy. Soc. Med.*, Aug., 1965, 58, 629-630. (From: Royal Infirmary, Edinburgh, Scotland.)

The author discusses the clinical trial to assess the results of radical mastectomy alone versus those obtained with simple mastectomy combined with radiotherapy.

He points out the problems of such a trial in its conception, execution and evaluation.—Luther W. Brady, M.D.

Galton, D. A. G. Clinical trials in progress: leukaemia and multiple myeloma. *Proc. Roy. Soc. Med.*, Aug., 1965, 58, 630–632. (From: Chester Beatty Research Institute, London, England.)

The author discusses the clinical therapeutic trials

in leukemia. Seven were started: 2 being completed, 1 redesigned and 4 continue in progress.

A total of 117 patients with chronic granulocytic leukemia has been studied using two groups—one with busulphan and the other with splenic irradiation or P<sup>52</sup> intravenously.

Comparative trials in acute leukemia in adults and children have begun, comparing 6-mercaptopurine and high and low dose prednisone.

In myelomatosis the trials are between melphalan and cyclophosphamide.

The author discusses the problems in such trials including criteria of eligibility, diagnostic criteria, analysis of results and organizational problems.—

Luther W. Brady, M.D.

McEwen, D. J. B. Clinical trials in progress: radiotherapy and hyperbaric oxygen. *Proc. Roy. Soc. Med.*, Aug., 1965, 58, 632. (From: St. Mary's Hospital, Portsmouth, England.)

The author describes the clinical trial in progress at St. Mary's Hospital, Portsmouth, to answer the question: "Is the survival time of certain patients with carcinoma of the lung or of the urinary bladder, treated with megavoltage radiotherapy in oxygen at a pressure of 3 atmospheres absolute, as good as, better than, or worse than that of a similar group of patients treated in the same way in air?"

In 12 months, 27 patients have been treated in the lung trial and in 7 months, 14 patients in the bladder trial.

The techniques and problems are discussed.— Luther W. Brady, M.D.

RENDALL, MAX, and PATEY, DAVID H. Efficiency of axillary clearance in operations for carcinoma of the breast: lymphangiographic observations. *Brit. J. Surg.*, Aug., 1965, 52, 565-568. (From: Department of Surgical Studies, Middlesex Hospital, London, England.)

In 1948, Patey and Dyson advocated a modification in the standard radical mastectomy procedure which would preserve the pectoralis major muscle. They believed that complete axillary lymph node clearance could be obtained without sacrificing the pectoralis major muscle. A number of British surgeons has adopted this procedure with satisfactory results. In the United States there is persistent doubt on the efficiency of axillary clearance without removal of the pectoralis major muscle. It is now possible to demonstrate by lymphangiography that axillary lymph nodes can be almost completely removed while preserving the pectoralis major muscle.

In 1963, Auchincloss advocated preservation of both pectoralis muscles. In order to study his method, 3 cases of carcinoma of the breast in which there was no evidence of axillary lymph node involvement were operated according to his plan. Lymphangiography was performed before and after surgery. It was determined in all cases that good axillary clearance was obtained, but the nerve supply to the pectoralis minor muscle was destroyed, leaving no function in the preserved muscle. This seemed to speak against preservation of this muscle at the expense of suboptional axillary clearance.

Lymphangiography is a useful test of the efficiency of lymphatic clearance operations.—Richard E. Kinzer, M.D.

BICKENBACH, W., LOCHMÜLLER, H., and FLACH, D. Five-year symptom-free survival and excess mortality in patients with endometrial carcinoma. *German Med. Monthly*, Sept., 1965, 10, 259–262. (From: Frauenklinik und Hebammenschule der Universität München, Germany.)

It is usual to report results of treatment of genital carcinoma in terms of 5 and 10 year survivals. This includes all patients, whether they have been lost to follow-up or died of some unrelated malady.

The authors suggest that a supplemental report is sometimes necessary. In support of this, 783 patients treated for endometrial carcinoma from 1948 to 1958 were reviewed. An absolute cure rate of 62 per cent was found. The patients were treated in one of two ways: (1) radiotherapy alone, including radium and external irradiation; (2) total hysterectomy followed by radium and external irradiation. The second group comprised 668 patients with a 5 year cure of 80.9 per cent; the first had 115 patients with a cure rate of 58.8 per cent.

They conclude that the apparent disparity in cure rates arises from the fact that the surgery group included a greater number of younger women. In poor risk cases, therefore, it is not necessary to insist on surgery for a commendable cure rate.—W. J. Carmoney, Jr., M.D.

PACK, GEORGE T., and DAVIS, JEFF. Radiation cancer of the skin. *Radiology*, Mar., 1965, 84, 436-441. (From: Pack Medical Foundation, New York. N. Y.)

The incidence of radiation cancer of the skin is reported in a series of 59 patients. These were divided into 2 groups: (1) 31 patients in whom the cancers developed after a previous course of radiotherapy for benign dermatoses or malignant tumors; and (2) 28 patients in whom radiation cancer developed as a result of adventitial exposure.

In the first group the prior therapeutic roentgenray treatments consisted of 6-12 superficial doses within a period of 6 months to 1 year. In 2 patients, single doses were given for benign dermatitis.

The second group consisted of patients engaged in professional use of roentgen rays and radium from 2-43 years.

The age incidence of cutaneous radiation carci-

noma cases was between 50 to 70 years, with the average being 43 to 49 years. The occupational carcinomas were seen in patients between 60 to 80 years. The males were affected more often. Thirty-eight had cancers on the hands. No predominance of cancers of left hand was observed in the cases of physicians who had chronic exposure.

The latent period for development of cancer had been 23 years in cases of therapeutic irradiation and 16 years in cases of occupational exposure. In 40 per cent of the patients the cancers were multiple.

The most common lesion in the series was the squamous cell carcinoma (50 cases). There were 4 basal cell carcinomas and 4 spindle cell carcinomas and 1 case of basisquamous cell carcinoma. The incidence of distant metastases was 6 in 59 cases.

Treatment carried out in the series consisted of excision of areas of chronic radiation dermatitis and carcinoma followed by skin graft. Plastic repair was carried out in 4 cases.

Six patients died of metastases, I died of aleukemic leukemia.—K. K. N. Chary, M.D. F.F.R.

#### RADIOISOTOPES

Quinn, James L., III, Ciric, Ivan, and Hauser, William N. Analysis of 96 abnormal brain scans using technetium 99m (pertechnetate form). J.A.M.A., Oct. 11, 1965, 194, 157–160. (Address: Dr. Quinn, 250 E. Superior Street, Chicago, Ill.)

Technetium 99m, in the pertechnetate form, was evaluated as an agent for brain scanning. Te<sup>99m</sup> has a physical half life of 6 hours and no particulate radiation emission; large doses (10 to 15 mc) were administered without excessive patient irradiation. The scanning speed was increased and a single view of the brain recorded in 5 minutes. Because pertechnetate is cleared slowly from the blood, the normal intracranial vascular structures, not seen with chlormerodrin Hg<sup>197</sup> and chlormerodrin Hg<sup>203</sup>, are depicted on the scan.

In our study of 625 patients, 54 of 65 patients with proved intracranial neoplasia had positive results on brain scans. Forty-one patients with a variety of non-neoplastic intracranial diseases had positive scans. Tc<sup>99m</sup> in the pertechnetate form was found to be as nonspecific as chlormerodrin Hg<sup>197</sup> and chlormerodrin Hg<sup>208</sup> in outlining intracranial disease.—
Merle K. Loken, M.D.

Loken, Merle K., Telander, Gerald T., and Salmon, Robert J. Technetium 99m compounds for visualization of body organs. J.A.M.A., Oct. 11, 1965, 194, 152–156. (Address: Dr. Loken, University of Minnesota Hospitals, Minneapolis, Minn.)

Technetium 99m is readily available from a Mo<sup>39</sup>-Te<sup>99m</sup> generator and possesses nearly ideal physical

properties for organ visualization when used with either a scanner or scintillation camera. Brain phantom studies indicate that comparable resolution of pseudotumors containing Tc<sup>94m</sup> may be obtained with either unit.

Studies of more than 100 patients suspected of having brain lesions indicated that  $Tc^{99m}$  in the pertechnetate form is satisfactory for cranial scintiphotography. Albumin is tagged radioactively with  $Tc^{99m}$  in our laboratories and used for placental localization. A colloid of this material is obtained by controlling heating. Small particles  $(200 \mu)$  are used for visualization of liver and spleen. Macroaggregates  $(50 \mu$  to  $100 \mu)$  obtained by continued heating are used for lung scintiphotograms.

Animal and human studies with preparations of albumin labeled with radioactive technetium (Tc<sup>99m</sup>) have yielded good results with no adverse side effects noted.—Eugene Gedgaudas, M.D.

GROS, CH. M., SCHNEEGANS, E., WACKENHEIM, A., OBERSON, R., and HAARSCHER, A. M. Scintigraphie de l'hématome sous-dural du nourrisson. (Scintigraphy in the diagnosis of subdural hematoma in the infant.) J. de radiol., d'électrol. et de méd. nucléaire, Aug.—Sept., 1965, 46, 453–456. (From: Service Central de Radiologie et de l'Institut de Puériculture des Hospices civils de Strasbourg, France.)

Because of the difficulties encountered in performing pneumoencephalography and cerebral angiography in the infant, the authors stress the value of scintigraphy (cerebral scanning) with radioactive iodinated human serum albumin (RISA).

Fifty to seventy microcuries are injected through the anterior fontanelle. This is followed by rapid diffusion of the isotope into the hematoma.

The examination is simple, innocuous, and of a high degree of accuracy. It gives sharp delineation of the subdural hematoma, its extent, and distribution. Furthermore, the procedure offers a simple method for follow-up to demonstrate the regression of the hematoma.

The authors report on 7 examinations of subdural hematomas in 5 infants; 2 had bilateral hematomas.

The accuracy of the diagnosis and the ease of examination are superior to pneumoencephalography and angiography.

Reproductions of 5 illustrative brain scans accompany this article.—William H. Shehadi, M.D.

HARTOG, M., DOYLE, F., FOTHERBY, K., FRASER, RUSSELL, and JOPLIN, G. F. Partial pituitary ablation with implants of gold-198 and yttrium-90 for Cushing's syndrome with associated adrenal hyperplasia. *Brit. M. J.*,

Aug. 14, 1965, 2, 392-395. (From: Departments of Medicine, Radiology, and Chemical Pathology, Postgraduate Medical School of London, London, England.)

The authors have been treating patients with Cushing's syndrome due to bilateral adrenal hyperplasia by means of implantation of Au<sup>198</sup> and/or Y<sup>90</sup> into the pituitary. This method allows for delivery of a higher dose than can be obtained by external roentgen-ray therapy. The rationale for treating the pituitary is based on the known association of Cushing's syndrome with overt pituitary tumor and the fact that some remission is obtained by the use of deep roentgen-ray therapy to the pituitary in about ½ of the cases of Cushing's syndrome with bilateral adrenal hyperplasia.

The article reviews the procedures used to establish the diagnosis of Cushing's syndrome due to bilateral adrenal hyperplasia. It shows the value of these procedures in estimating the response following the implant.

The technique of implantation has been described previously by the authors.

Twenty patients were treated. Eight had Au<sup>108</sup> implants planned to deliver 10,000 rads to the periphery of the pituitary. The others had combined implants of Au<sup>108</sup> and Y<sup>00</sup>, each source planned to deliver 5,000 rads to the periphery of the gland. Five patients had several implants with doses ranging from 10,000 to 100,000 rads.

In evaluating the results "satisfactory" is defined as disappearance of symptoms, normal facies, improved glucose tolerance test and normal 17 oxygenic steroids. A "partial" response is partial remission of signs and symptoms or a satisfactory response that is only temporary.

Patients were followed from 3 to 54 months with a mean of 15 months. Of the 20 patients treated, 14 had no obvious pituitary tumor. Of these 14, 8 showed a satisfactory response and 4 a partial response. Two patients were re-implanted, one obtaining a satisfactory response.

Six patients had obvious pituitary tumors. Four showed a partial response, and 2 had no response. Three patients were re-implanted with no response in 2 and the third not reported.

The main complication was cerebrospinal fluid leakage in 4 patients, 3 of whom had obvious pituitary tumors and 1 had an anomaly of the subarachnoid space. One patient developed a visual field defect.

The only evidence of hypopituitarism was in I patient who developed amenorrhea.

The authors feel that higher initial doses of radiation will result in a higher incidence of remissions. They plan to use Y<sup>90</sup> alone, delivering a dose of 50,000 rads to the periphery of the gland in cases with pituitary tumors and 20,000 rads to those without obvious tumors.—William Levy, M.D.

Hartoo, M., Doyle, F., Fraser, Russell, and Joplin, G. F. Partial pituitary ablation with implants of gold-198 and yttrium-90 for acromegaly. *Brit. M. J.*, Aug. 14, 1965, 2, 396-398. (From: Departments of Medicine and Radiology, Postgraduate Medical School of London, London, England.)

The authors report their experience in treating acromegaly by implantation of radioactive seeds into the pituitary. The objective of this treatment is to destroy the overactive growth hormone-secreting cells without impairing pituitary function.

The patients were diagnosed and later evaluated on the basis of the clinical picture and various indirect measurements of growth hormone hypersecretion. These included the augmented insulin tolerance and prednisone glycosurin tests, serial photographs of the facies, hand volume determinations, cortical thickness of the metacarpals, and the 24 hour urine calcium excretion while on a low calcium diet. The relative value of these studies in assessing the activity of acromegaly is shown.

Twenty-four patients were studied following implantation. In most cases the transethmoidal route was used, with occasional use of the transnasal route. The procedure was controlled by fluoroscopy with image intensification.

Au<sup>198</sup> was implanted in 15 patients and combined implants of Au<sup>198</sup> and Y<sup>90</sup> were used in 6. In both groups a calculated dose of 10,000 rads to the periphery of the pituitary was given. Y<sup>90</sup> was used in 1 patient, giving a calculated dose of 20,000 rads to the periphery of the gland. Nine patients had second implants, with doses ranging from 1,000 to 100,000 rads.

The patients were followed from 4 to 48 months with a mean of 15 months. A "satisfactory" response is defined as the lost of symptoms, regression of acromegalic facies, normal insulin tolerance test, and normal or improved glucose tolerance test.

Of the 22 patients implanted, the response after the final implant was satisfactory in 13, partial in 6, and unchanged in 3.

Normal pituitary function was not impaired in 13 patients. Corticosteroid and/or thyroid dependence developed in 9, of whom 1 had deliberate total pituitary destruction and 5 had pituitary abscess.

Complications from a total of 39 implants in 28 patients consisted of 8 cases of pituitary infection, with 1 being fatal. Four patients developed cerebrospinal fluid leaks, 1 requiring surgical repair. Two patients developed visual field defects.

Implantation of radioactive seeds is compared with other methods of treatment of acromegaly. These consist of deep roentgen-ray therapy, excision of the tumor, total hypophysectomy, and high energy particle irradiation. On the basis of the relatively small number of cases reported, it appears that implantation offers the best results in terms of success-

ful remissions and preservation of pituitary function.

In order to reduce cerebrospinal fluid leaks, postoperative pituitary infection and hypopituitarism due to infection, the authors now use preoperative antibacterial nasal sprays and Y<sup>90</sup> alone, giving a calculated peripheral dose of 20,000 rads. The Y<sup>90</sup> may be self-sterilizing and the higher dose of irradiation is expected to yield an improved rate of remission.—William Levy, M.D.

GROS, CH. M., WACKENHEIM, A., VROUSOS, C., and SUBIRANA, M. La scintigraphie des espaces sous-arachnoidiens du canal rachidien. (Scintigraphy of the subarachnoid spaces of the spinal canal.) J. de radiol., d'electrol. et de méd. nucléaire, Aug.—Sept., 1965, 46, 457—464. (From: Clinique Neurologique et Service Central de Radiologie du C. H. U. de Strasbourg, France.)

Scintigraphy of the spinal subarachnoid space was first done by Bauer and Youl in 1953; subsequently, encouraging reports of the practical application of this procedure have appeared from Strasbourg in 1963.

During recent months, the authors have examined

70 patients with this procedure.

The technique calls for the use of radioactive iodinated human serum albumin (RISA) introduced into the subarachnoid space either by lumbar or suboccipital puncture. The procedure is painless. Rarely, there has been slight transitory meningeal reaction, not unlike that accompanying a routine lumbar puncture. The patient is kept fasting and from 100 to 200  $\mu$ c of RISA, depending on the weight of the patient, is introduced into the subarachnoid space. A scan is obtained 5 hours later, with the patient in the decubitus position. A delay of 5 hours ensures adequate diffusion of the radioactive material throughout the subarachnoid space, extending up to the intracranial cisterns. It is estimated that from 15 to 20 r reach the spinal column.

The scintigram adequately delineates the subarachnoid space from the cul-de-sac to the cisterna magna. The latter gives a slight triangular appearance on the dot scan at the level of the base of the skull. Slight widening on the scintigram is noted at the cervicodorsal junction, about the level of C7. Activity then is slightly decreased in the region of the upper dorsal spine, compared with the lower dorsal spine, because of the relative narrowness of the spinal canal. Lordosis of the lumbar area, especially when pronounced, is responsible for an area of decreased darkening on the scan. The cul-de-sac at the lumbosacral area presents variations in its appearance comparable to the recognized anatomic variations at this level.

Illustrations of the abnormal include medullary atrophy, where there is dilatation and widening of the perimedullary space, with relative increase in activity; and syringomyelia, with marked widening at the cervico-dorsal area. In the presence of incomplete or complete obstruction, there is complete arrest of the flow of RISA with sharp delineation of the point of obstruction.

The scans, or scintigrams, of several cases of complete blockage due to herniated disk, or other causes, are presented with comparison studies confirming the site of complete blockage, demonstrated by air and lipiodol myelography.

The full value and application of this procedure as compared with positive or negative myelography

call for further exploration.

Ten figures illustrating scans, with companion myelograms, accompany this interesting presentation.—William H. Shehadi, M.D.

ARIEL, IRVING M. An aid for determining treatment of liver cancer by combined hepatic gammascanning. Surg., Gynec. & Obst., Aug., 1965, 121, 267-274. (From: The Pack Medical Foundation, Inc., New York, N. Y.)

Combined hepatic scintiscans utilizing both iodine 131 rose bengal and gold 198 are reported to be beneficial in evaluating patients for hepatic cancer chemotherapy. I<sup>131</sup> rose bengal is cleared by the liver parenchymal cells and excreted in the bile. Au<sup>198</sup> is concentrated by the hepatic reticuloendothelial cells. The appearance of a rose bengal I<sup>131</sup> scan is dependent on hepatic function, whereas an Au<sup>198</sup> scan will reveal liver detail independent of function. The combination of these scans then gives an indication of hepatic function as well as replacement of hepatic tissue. Liver diseases that result in vascular compromise such as cirrhosis, will cause decreased concentration on both scans.

When contemplating hepatic interarterial infusion of cancer chemotherapeutic drugs, one must determine the functional state of the liver since their use is contraindicated in severe hepatocellular damage. The combination of rose bengal I<sup>131</sup> and Au<sup>198</sup> scans can be used to differentiate between an otherwise normal

liver with metastasis and a liver with associated severe parenchymal damage. Liver function tests cannot always be relied upon to make this differentiation. The rose bengal I<sup>31</sup> scan can be used to follow the progress of chemotherapy and any correction for vascular compromise can be assessed by combination with the Au<sup>198</sup> scan. Furthermore, the two scans will rule out the hepatic origin of a space-occupying lesion if it is shown by both isotopes.

It is suggested that the poor results and the high mortality from interarterial administration of chemotherapeutic agents in the liver may be due to improper evaluation of the liver disease.

The author's experience with 6 patients is given.— Evrett E. Smith, M.D.

Paredes, Santiago, Comer, Frank, Rubin, Sidney, Adler, Federico, and Peltier, Leonard F. Fat embolism: distribution of fat tagged with I<sup>131</sup> within the body of the rat at various times following intravenous injection. J. Bone & Joint Surg., Sept., 1965, 47-A, 1216–1220. (From: Menorah Medical Center and University of Kansas Medical Center, Kansas City, Kansas.)

The distribution of intravenously injected I<sup>131</sup> triolein was determined in 18 rats. The radioactivity in tissues was measured at intervals up to 144 hours.

Lungs, thyroid, brain, liver, kidneys, heart, whole blood and muscle were studied.

Early distribution was marked in lung tissue, declining gradually after 24 hours. Parallel with this decline there was a rise in the radioactivity of the thyroid gland, indicating a breakdown of the triolein to iodide.

Three scan-radiograms are shown illustrating the distribution pattern in the lungs and thyroid gland. All other tissues exhibited low radioactivity.

The observations made on the distribution of triolein tagged with I<sup>131</sup> in rats is discussed in the light of traumatic fat embolism in the human.— Yosh Maruyama, M.D.



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# RECURRENT GIANT-CELL TUMOR OF THE PROXIMAL TIBIA: RESECTION-RECONSTRUCTION

 Preoperative anteroposterior and lateral radiographs show the large recurrent giant-cell tumor of the right proximal tibia.





es skin incision including elliptical renof the previous biopsy scar.

-bilization of the peroneal nerve and are of the anterior tibial vessels.

section of the proximal fibula and ction of the fibula. (The proximal poras removed and longitudinally bisected aft material.)

e patella has been reflected proximally knee joint entered. The proximal tibia ilized by sectioning the ligaments and e of the knee joint.

entire proximal tibia has been mobind is divided at a level well below the (Note the inclusion of the overlying sues with the specimen.)

e gross appearance of the bisected respecimen shows extensive recurrent with adequate margins throughout.

e distal femur has been mobilized and stal articular cartilage removed. The longitudinal hemisection of the distal is being removed for bone graft.

premeasured Kuntscher intramedulod is driven through the extent of the ning femur and tibia providing solid n to the extremity.

the femoral graft is reversed and fixed the with screws. The split fibular grafts were into the medial femoral metaphyee postoperative radiographs.) Bonenaterial obtained from the patella and accrest is subsequently packed in the ming defect.

perative area immediately following losure. (Note suction drainage tubes in and the wire sutures in the skin.)

nteroposterior and lateral radiographs ig the immediate postoperative appear-(Note solidity of fixation and volumiquantity of bone-graft material.)





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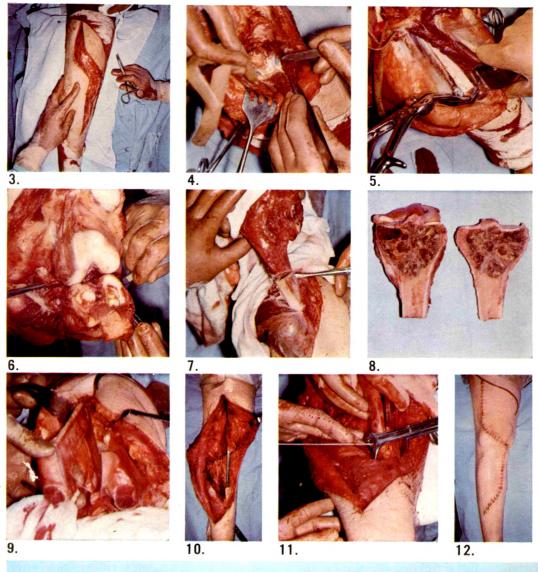
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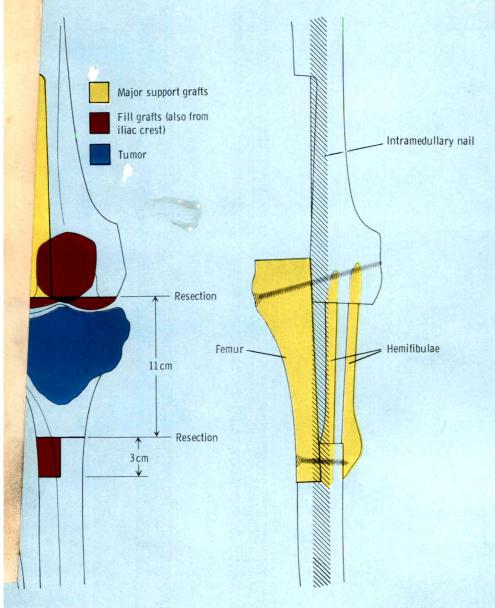




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right proximal tibia in December, 1963. The initial treatment consisted the placement of autogenous bone graft. Eight months later, July, 1964, and swelling brought her to surgery. Diagnostic evaluation revealed a large cell tumor. The therapeutic program proposed was segmental resection onstruction of the extremity.

imatic representation of the proposed resection and reconstruction, anterior aspect.



For further information . . . TURN PAGE

# Neuroendocrinology

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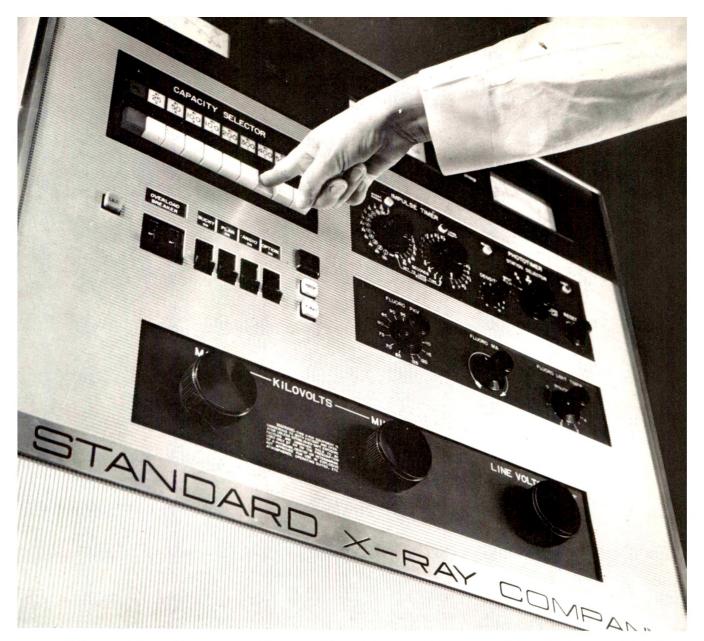
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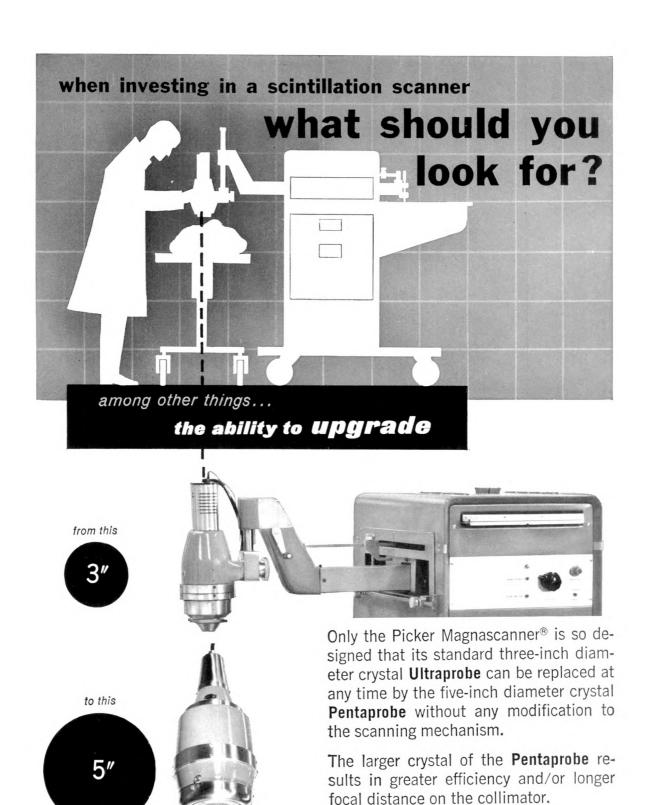
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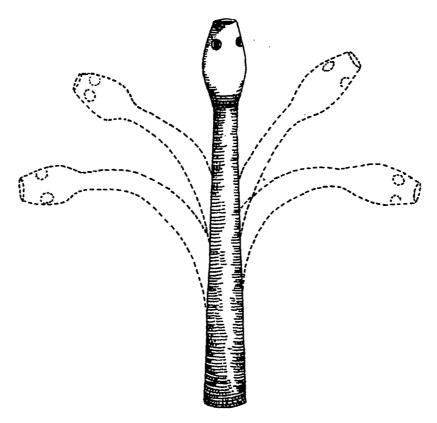
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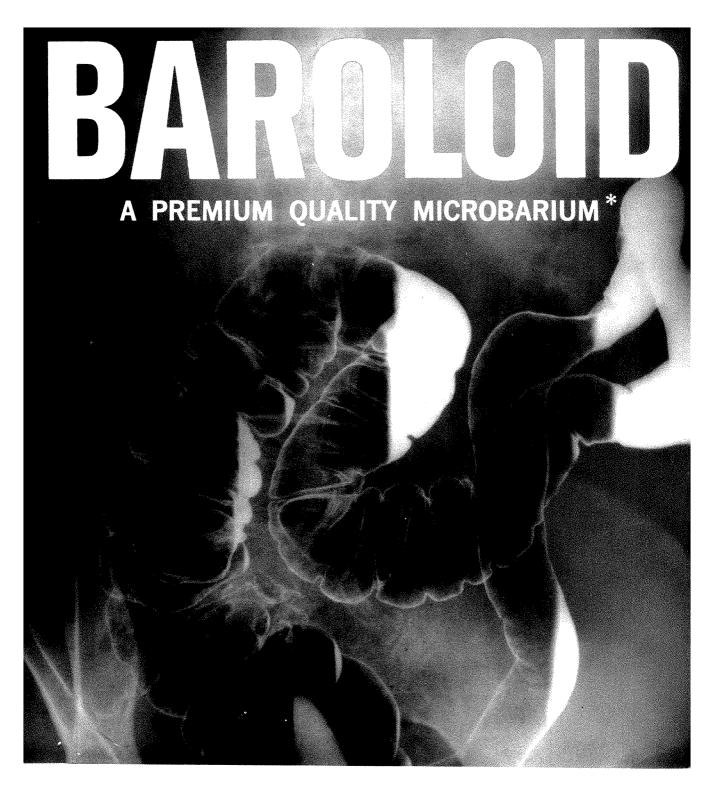
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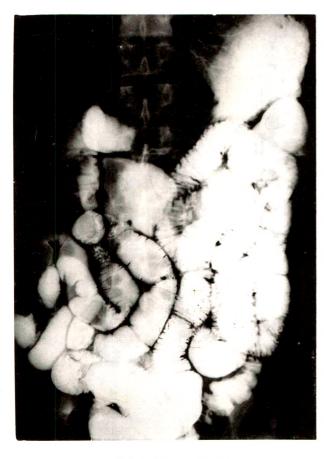
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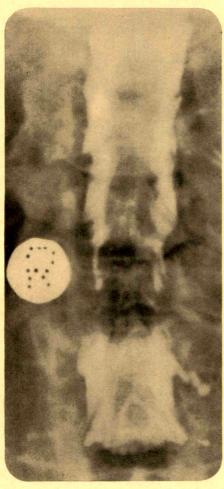
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## THE AMERICAN JOURNAL ROENTGENOLOGY

### RADIUM THERAPY AND NUCLEAR MEDICINE

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#### CINERADIOGRAPHY IN NORMAL AND ABNORMAL WRISTS\*

By RICHARD ARKLESS, M.D.† SEATTLE, WASHINGTON

INERADIOGRAPHY has been valu-Cable in understanding the dynamic interactions of the carpal bones in normal and abnormal states. Studies of standard roentgenograms in various projections, of surgically exposed wrists and of autopsy specimens all have added to the basic understanding of abnormalities in the wrist,4 but cineradiographic studies add to the study of the live patient performing acts similar to those which cause symptoms. They help reveal how the distribution of stress is altered in abnormal states, help predict the possibility and location of future arthritis, help explain the source of pain, and help determine the type of treat-

The normal motions in the wrist will be described. This will be followed by descriptions of the cineradiographic abnormalities present in 3 patients with traumatic subluxations of the navicular, and I patient with bilateral, old Kienböck's aseptic lunate necrosis as well as similar subluxations. It will be shown how these subluxations are interrelated to the "clicking" lunate (in which the lunate "snaps" in and out of joint) as seen in 3 patients, and the "clicking" navicular (where the "snapping" involves the navicular) in 2 patients. The state of the united navicular will then be discussed (6 further patients).

The preliminary studies were done with 16 mm. film; to achieve finer detail, subsequent studies with 35 mm. film were performed using a 0.5 mm. focal spot and 3 inch output phosphor. Thirty-six abnormal and 40 normal wrists have been studied (38 patients).

#### THE NORMAL WRIST

The wrist was firmly fixed so motions in different planes could be individually studied. The wrist can be considered as having a proximal "cup" of 3 bones, the navicular, lunate and triquetrum, which articulates with the radius and which contains the distal "inset" of the capitate and hamate (Fig. 1). On ulnar deviation, the navicular is exposed in full profile and the navicular-

<sup>\*</sup> Presented at the Thirteenth Annual Meeting of the Association of University Radiologists, Seattle, Washington, May 13-16, 1965. From the Department of Radiology, University of Washington Hospital, Seattle, Washington. † Winner of Memorial Medal Award of the Association of University Radiologists, 1965.

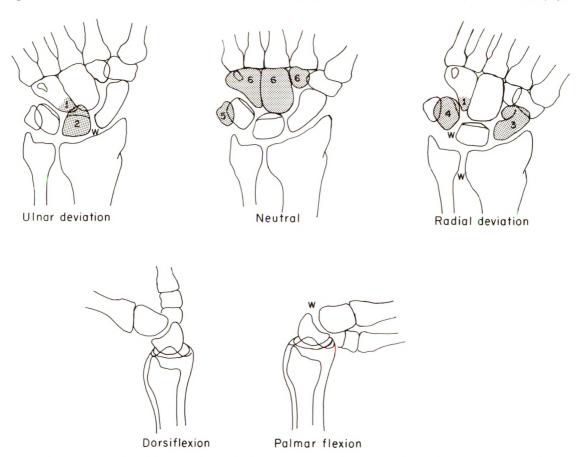


Fig. 1. The normal wrist, 1 = tip of hamate, displaced from lunate on radial deviation but abutting it in ulnar deviation; 2 = lunate being rotated into palm by the tip of the hamate; 3 = distal end of navicular rotating into palm. Note how greater multangular slides over it; 4 = triquetrum sliding distally along the lunate; 5 = pisiform (a sesamoid bone) moving semi-independently of other carpals; 6 = rigid distal "inset" (hamate-capitate-lesser multangular) whose motion determines in large part, the complex motions of the proximal carpal "cup" (navicular, lunate and triquetrum); w = those joints which widen most perceptibly.

lunate joint widens slightly. On radial deviation, the distal end of the navicular partly rotates into the palm with the greater multangular sliding down over it, and the lunate-triquetrum joint widens slightly. These joint widenings are seen in all normal wrists and are accentuated by slight passive stress. The triquetrum does not articulate with the radius and is separated from the ulna by a meniscus. In radial deviation, the triquetrum slides peripherally in relation to the lunate and stays in close approximation to the hamate.

Whereas the proximal carpal "cup" forms a supple bony triad, the distal "inset" moves as a unit with no motion in the

capitate-hamate joint. The distal "inset" rotates within the cup, such that in radial deviation the space between the tip of the hamate and the lunate widens. In ulnar deviation the hamate abuts on the lunate, slides along it a short distance and is associated with palmar displacement of the lunate. It is the gliding motion of the "inset" that determines, to a large extent, the changes seen in the "cup."

The remaining 3 carpals are of less importance in this wrist motion. The lesser multangular, like the hamate, is a fixed satellite on the capitate; these 3 bones (and the 2nd through 5th metacarpals) move as a single functional unit. The greater mult-

angular sits on the navicular, sliding down over it in radial deflation (vide supra). The pisiform (a sesamoid in the flexor carpi ulnaris tendon) is governed mostly by the motion of this tendon; this can be demonstrated by firmly holding the wrist and having the fingers spread apart and together whereupon the pisiform moves proximally and distally in relation to the other carpals.

Dorsopalmar wrist motion shows the lunate to rotate on the radius and the capitate to rotate in the cup of the lunate (Fig. 1). The degree to which the lunate may palmar-flex or dorsiflex varies in different normal people. Opening of the dorsal aspects of the lunate-radius and capitate-lunate joints occurs in palmar flexion, and vice-versa. Passive stress accentuates this.

Thumb motion was tested with the hand fixed in the position of function. Although there is free motion in the interphalangeal, metacarpophalangeal and carpometacarpal joints, there is virtually no motion of the great multangular on the navicular, and none of the navicular in the wrist. This concept is important since the question has long been raised whether or not the thumb should be immobilized by a cast for a navicular fracture.<sup>1</sup>

Pronation-supination was tested by fixing the hand to the examining table and having the patient rotate his body around his wrist. It was found that there is virtually no motion of the carpals here. The ulna turns freely in the radio-ulnar joint. pistoning back and forth several millimeters in relation to the radius. In some patients it does seem to transmit slight pressure into the carpals through the triquetrum but the navicular seems virtually unaffected. It would seem that a navicular fracture cast need not restrict pronation-supination for proper healing to occur. These concepts will be developed further below.

#### NORMAL VARIATIONS

The extent of the various movements described above varies from patient to

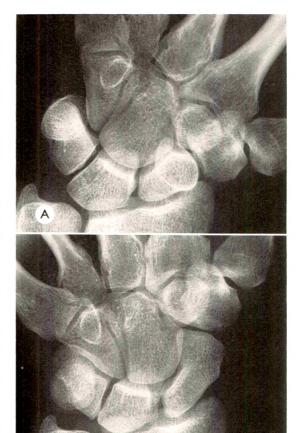


Fig. 2. (A and B) Normal variation of wrist dynamics. Cine studies revealed diminished movement of the lunate with compensatory excessive rotation of the distal navicular end into the palm. No history of injury.

patient. Occasionally, one notes excessive variations of normal, however, and 3 such instances will be described.

A young nurse demonstrated an interesting variation (Fig. 2, A and B) in that the lunate in her normal wrist did not have the usual deflection during radial deviation. As a compensatory mechanism, the distal end of the navicular rotated into the palm more than the average amount, thus permitting the distal "inset" to carry out its normal range of motion.

A 30 year old healthy Negro female with asymptomatic wrist joint laxity had similar excessive navicular rotation. However, instead of restricted lunate motion





Fig. 3. (A and B) Bilateral subluxated naviculars. Vague history of prior trauma. In addition to slight lunate sclerosis and navicular flattening, note the wide navicular-lunate joint. Cine studies showed the distal "inset" to enter this space during ulnar deviation and nearly articulate with the radius.

she had a slight increase, and her intercarpal joints could be spread more than the average patient's. Similar laxity was also present in the radio-ulnar joint in pronationsupination studies.

A third patient had congenital fusion of the lunate and triquetrum. As expected, the motion of the distal "inset" within the proximal "cup" was restricted. He was asymptomatic.

#### SUBLUXATED NAVICULAR

Increase in the space between the navicular and lunate is called either subluxation or rotational dislocation of the navicular.<sup>2,3</sup> Although usually traumatic, it can result from rheumatoid arthritis. Four post-traumatic subluxations will be described to demonstrate that similar plain film appearances have different inherent dynamic aberrations when studied cineradiographically.

A middle-aged male presented with a several week history of pain in one wrist following trauma to the ulnar side. Prior history of wrist injury was vague (related to claim for workman's compensation?). Both wrists showed identical changes on routine roentgenograms: slight sclerosis of the lunates, flattening of the proximal ends of the naviculars, and widening of the navicular-lunate joints (Fig. 3, A and B). It is notable that he has been continually employed at jobs requiring strenuous use of both hands. Cineradiography revealed the abnormal lunate-navicular joint widening to be accentuated in ulnar deviation, allowing the distal "inset" to enter this space such that the capitate nearly articulated with the radius.

A second patient, following a fall on his palm, was noted to have a similarly widened navicular-lunate space. Cineradiography here showed changes different from those of the previous patient. Here, the proximal end of the navicular undulated in and out of palmar deviation twice during a single radio-ulnar deflection of the wrist (in the former patient, there was only a smooth accentuation of the joint widening in this motion). Several months after unsuccessful surgery, the wrist was re-examined (Fig. 4). The double undulation was no longer seen, but the proximal part of the navicular still moved in and out of the palm and the navicular-lunate joint remained wide. The subluxation was most pronounced midway between radial and ulnar deviation (in the first patient it was most pronounced in extreme ulnar devia-

A third patient (Fig. 5), had a history and routine roentgenograms similar to the last. He was examined following unsuccessful surgery and similar excessive motion of the proximal half of the navicular was revealed. The abnormal motion of the navicular was not as marked as in the former, however. This suggests that different degrees of ligament injury can show similar routine roentgenographic changes, yet be shown to be different on cineradiography.

The fourth patient was found to have a subluxed navicular following reduction of a depressed comminuted distal radial fracture. The subluxation was again accentuated by ulnar deflection of the wrist but was less pronounced than in the above patients. Reduction was affected by placing traction on the wrist and putting the wrist in slight radial deviation.

In the patients described above, the concept that a cast for a navicular injury need not restrict pronation-supination or thumb motion was explored. These motions were studied in a fashion similar to the controls. Even though the navicular had increased freedom of motion during radio-ulnar and dorsopalmar movements, active thumb motion (or pressure of the thumb on the middle finger) caused no perceptible move-



Fig. 4. Post-traumatic subluxated navicular. Original operation unsuccessful (note displaced pin). Pre- and post-operative cineradiograms showed the proximal navicular end to undulate in and out of the palm on radio-ulnar deflection. The dynamics were different in the 2 studies, however (see text).



Fig. 5. Post-traumatic subluxated navicular. Dynamic alterations were different from those in the former patient on cine studies.

ment of the navicular. The same virtual absence of navicular movement in the wrist was found in pronation-supination studies. It was noted in the second patient (studied pre- and post-operatively) that following the unsuccessful surgery, the greater multangular moved slightly on the navicular with movements of the thumb; the navicular itself still remained immobile. The necessity of restricting thumb motion and pronation-supination by a cast for navicular injuries is therefore questioned. Studies on ununited navicular fractures reported below support this.

#### UNUNITED NAVICULAR FRACTURES

A young Navy man sustained a fractured navicular which remained clinically ununited following many months in a cast (Fig. 6). Cineradiograms showed the fracture line to spread slightly on ulnar deflection of the wrist. On radial deflection, the distal fragment impacted itself into the proximal one. The impaction was most pronounced on the proximal side of the fracture. The nonunion was confirmed at surgery the next day.

A second patient, a college student, had similar routine roentgenographic findings following treatment for a similar fracture. The cineradiograms were similar to those of



Fig. 6. Ununited navicular fracture (surgically confirmed). Cine studies revealed the fracture fragments to be distracted in ulnar deviation. Although slight radial deviation caused impaction, extreme deviation led to malalignment of the impacted fragments.

the first patient. Since he was asymptomatic, no further treatment was felt indicated. Several months later, routine roentgenograms showed the fracture to be healed; cine-studies were normal at this time. A third patient revealed similar cine changes. Unfortunately, he was lost to follow-up.

Two further patients with clinically and roentgenographically ununited navicular fractures had similar dynamic alterations. But the sixth patient who had plain roentgenograms showing an apparent non-union had a virtually nonpainful wrist with cineradiograms failing to demonstrate motion; the patient had had a bone graft previously for this nonunion and it is thought some bridging at the fracture site may explain the lack of both symptoms and fracture site motion.

Except for this last patient, cineradiograms demonstrated motion at the fracture site. Pronation-supination and thumb motion studies were also done. The results were as in normal patients and patients with subluxated naviculars: no motion of the navicular in the wrist, virtually no motion of the greater multangular on the navicular, and (more important) no de-

tectable motion at the fracture line. This is further support for the concept that a navicular fracture cast need not prevent pronation-supination or restrict thumb motion. The hand should probably be casted in the position of function and in slight radial deviation.<sup>1</sup>

#### THE "CLICKING" WRIST

The patient described above with unusually lax ligaments had trauma to the back of her opposite hand, following which she noted a "clicking" sound and an aching in her wrist on wringing out clothes. Although orthopedic consultants thought this click was secondary to the loose radioulnar joint, cineradiography during pronation-supination showed the click was from spontaneous palmar subluxation and reduction of the lunate and proximal end of the navicular. This occurred at the time when the hamate abuts on the lunate (the pronation-supination was combined with slight radio-ulnar wrist deviation in this study to mimic the action of wringing out clothes).

A young army recruit had a similar "clicking" wrist with similar spontaneous subluxation and reduction of the lunate and proximal navicular on cineradiograms. His wrist differed in two respects. First, radio-ulnar deviation alone caused the subluxation. Second, dorsopalmar movements showed the lunate to move in a paradoxical manner; during dorsiflection, it rotated as if the hand were being palmar-flexed, and vice versa.

In a third patient (Fig. 7), a teenage boy who had a distal ulnar resection to restore pronation and supination (limited subsequent to malunion of a distal radial fracture), the lunate also "snapped" in and out of joint, carrying with it the adjacent parts of the navicular and triquetrum. Again, this subluxation occurred at the time when the tip of the hamate exerted pressure on the lunate. As in the other 2 patients, there was no demonstrable plain film abnormality.

The interrelation of "clicking" wrists

and wrists with subluxated naviculars was shown by the third patient described above with a subluxated navicular. On ulnar wrist deviation, as the hamate came into contact with the lunate, the latter sprung part way into the palm. As with the previous 2 wrists, this was associated with an audible "click." Spontaneous reduction occurred on bringing the hand back to neutral position.

Two other patients with aching in the wrist and an unexplained "click" with wrist movement were found to have a snapping motion of the navicular wherein the navicular lifted off the radius a millimeter or so and, on passing the abnormal spot (cartilage rent?), snapped back into its normal position. The abnormality occurred at different times of the wrist motion cycle in the 2 wrists. Both had normal routine roent-genographic studies.

It is noteworthy that in none of these 6 cases was the etiology of the "click" diagnosed on physical examination by orthopedists or on routine roentgenograms. In 1 patient, it was misdiagnosed as being from a loose radio-ulnar joint.

Comment. There has been no attempt to reproduce the individual frames of the cineradiographic strips in this article. This is because the changes described here are clearly demonstrable in the motion picture but are not fully appreciated in viewing individual sequential frames.

#### DISCUSSION

Cineradiography is a valuable addition to the study of selected cases of wrist injury. The wrist can be considered as being composed of a proximal supple "cup" of the navicular, lunate and triquetrum which sits on the radius and contains the rigid distal "inset" of the capitate and hamate. The motion of the "inset" helps change the shape and position of the members of the "cup." When there is a disturbance of the interrelationships of the carpal bones, there can be found a variety of alterations in wrist dynamics on cineradiography even though in different wrists the routine roent-



Fig. 7. "Clicking" wrist. Note distal ulna resection. As in the other 5 patients with similar problems, routine roentgenograms reveal no abnormality referable to the "clicking."

genograms appear similar.

Widening of the navicular-lunate joint (subluxed navicular) was examined in 4 patients. There were varied associated dynamic alterations demonstrable, involving not only the position and motion of the navicular and lunate, but also the secondary changes in position and interrelationships of the distal "inset." The "inset" can sometimes enter the abnormal joint space in the "cup."

A "clicking" in the wrist of I of the patients with a subluxated navicular was from transient displacement and reduction of the lunate. This case is a link between these 4 patients with subluxations and 3 others who had a "clicking" wrist as the only abnormality. Although these "clicking" wrists had subluxation and reduction of the lunate as a partial explanation of the phenomenon, there were again different dynamic alterations in the other carpals demonstrable on cine studies. In 2 other patients, the "click" involved abnormal dynamics of the navicular.

These studies have also been helpful in understanding the changes in ununited navicular fractures. Evidence gained here supports the concept that the best way to cast fresh navicular fractures is in the posi-

tion of function and in slight radial deviation.

The question of whether a navicular fracture cast should immobilize the thumb and/or prevent pronation-supination was also explored. Studies of thumb motion in all the normal and abnormal conditions described above (including ununited navicular fractures) fail to show that the navicular is moved by motion of the thumb or that anything but insignificant motion of the greater multangular on the navicular is effected. Pronation-supination studies also cause no navicular motion; only in some patients does the pistoning ulna exert any force on the ulnar side of the carpal "cup." Even in these patients, this is not felt to transmit sufficient stress to the navicular to interfere with fracture healing. It would seem a navicular fracture cast need only prevent wrist motion in the dorsopalmar and radio-ulnar directions; pronation-supination and unrestricted thumb movements should not interfere with healing.

#### SUMMARY

Preliminary cineradiographic studies of normal and abnormal wrist conditions have been made. Subluxated naviculars, "clicking" wrists, and ununited navicular fractures have been studied. The dynamic alterations differ from patient to patient in conditions which seem similar on routine roentgenograms. The information gained from cine examinations should be a valu-

able adjunct in pre-treatment diagnosis and planning. The concept of casting navicular fractures to allow both unrestricted thumb motion and unlimited pronation and supination has been explored and is felt to be valid.

Future studies of congenital abnormalities, of traumatic and rheumatoid wrist problems, and of adequacy of immobilization by various casts are in progress.

Department of Radiology University of Washington School of Medicine and University Hospital Seattle, Washington 98105

Without the cooperation of many orthopedists, both in the University Hospital system and in the community, this study would not have been possible. Technical assistance of Mr. S. Schumacher is acknowledged.

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#### CINEFLUOROGRAPHY AS A TEACHING INSTRUMENT IN THE UNDERGRADUATE COURSE IN MEDICAL PHARMACOLOGY\*

By THEODORE E. KEATS, M.D., DONALD Q. COCHRAN, M.D.,†
and THOMAS P. SWEENY, M.D.†
CHARLOTTESVILLE, VIRGINIA

IT IS the purpose of the authors to suggest the usefulness of cinefluorography as a teaching instrument in undergraduate medical education.

Cinefluorography has had wide application in clinical work, but despite its obvious advantages as a teaching modality, it has received scant utilization in the education of the medical student. The demonstration of functional anatomy, physiology, pathology and the pharmacologic action of drugs can be accomplished by this technique. Our effort is directed toward a demonstration of its potential in the teaching of pharmacology.

In its original form, this pilot program consisted of a series of cine strips produced by a standard fluoroscope image amplifier with 16 mm. cine attachment. The studies were performed on living dogs with the use of various contrast media and a variety of pharmacologic agents. Although virtually unlimited in its application, we have, to date, confined our experiments to those systems which lend themselves most readily to this technique and in which the student would find easy orientation. The results are presented as moving pictures and, of course, the still illustrations included here cannot do justice to the dramatic changes evident to the student observer. The following categories of pharmacologic agents have been presented, some of which lend themselves to still illustration.

A. Sympathomimetic Drugs

Epinephrine

Gastrointestinal Response (Fig. 1, A and B)

- 2. Vascular Response (Fig. 2, A and B)
- 3. Bronchial Response (Fig. 3, A, B and C)
- B. Adrenergic Blocking Agents

Ergotamine Tartrate (Fig. 1C)

Priscoline (Fig. 2C)

C. Cholinergic Drugs

Acetylcholine

- Gastrointestinal Response (Fig. 4, A and B)
- D. Cholinergic Blocking Agents

Atropine

- I. Gastrointestinal Response (Fig. 4C)
- E. Alkaloids of Opium

Morphine

- Gastrointestinal Response (Fig. 5, A and B)
- 2. Biliary Tract Response (Fig. 6, A and B)
- 3. Respiratory Response
- F. Morphine Antagonists

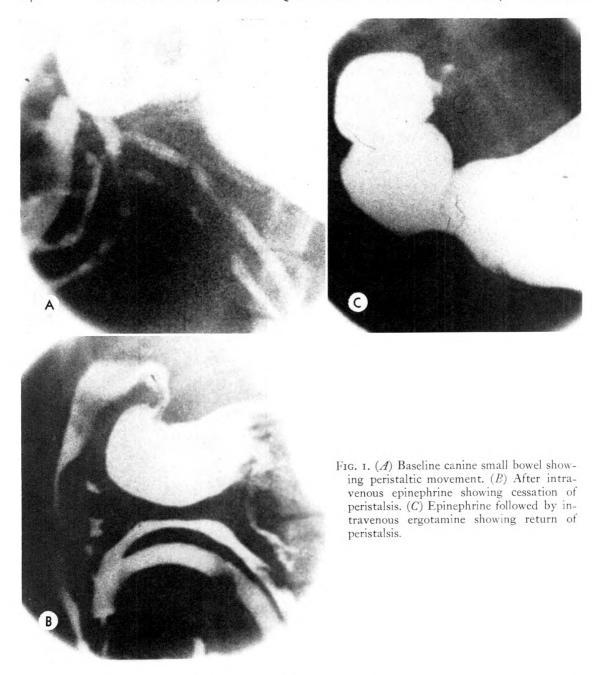
Nalorphine

- 1. Gastrointestinal Response (Fig. 5C)
- 2. Biliary Response (Fig. 6C)
- 3. Respiratory Response
- G. Histamine and Antihistamines
  - 1. Histamine and Benadryl (Fig. 7, A, B and C)
  - 2. Histamine and Epinephrine (Fig. 8, A, B and C)

#### COMMENT

Cinefluorography utilized in the manner illustrated, in our hands, provides an exciting and stimulating experience for the neophyte in medicine and lends easy correlation and retention of subject material with the visual images permitted by the roentgen technique. It is conceivable that this method could, at least in part, substitute for some of the laborious kymographic techniques which are currently in use and would permit the student to observe drug effects directly rather than

<sup>\*</sup> Presented at the Thirteenth Annual Meeting of the Association of University Radiologists, Seattle, Washington, May 13-15, 1965. From the Departments of Radiology, University of Virginia School of Medicine, Charlottesville, Virginia, and the University of Missouri School of Medicine, Columbia, Missouri.† Financial support from the Tobacco Industry Research Committee and The American Medical Association.

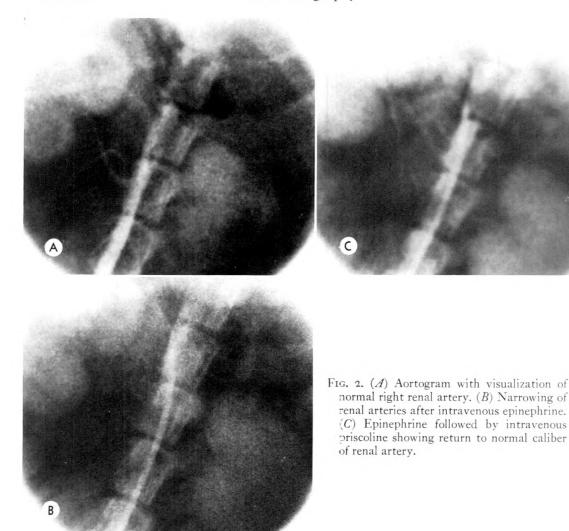


through an intermediate recording method. The addition of television monitoring and tape recording could, in turn, permit large group observations of the fluoroscopic image immediately and directly and obviate the delay inherent in cine processing.

We believe that the principles and appli-

cations of radiology are best taught in an integrated program closely related with the fundamental basic scientific disciplines. To be truly effective, such orientation should be continuous throughout the educational period.

When fully expanded, a program of



teaching with radiology in the basic sciences will permit the radiologist early contact with the student and will yield a student who is well acquainted with the roentgen method by the time he is fully involved in clinical work. As a by-product, this approach may enable teachers of radiology to interest students in radiology at

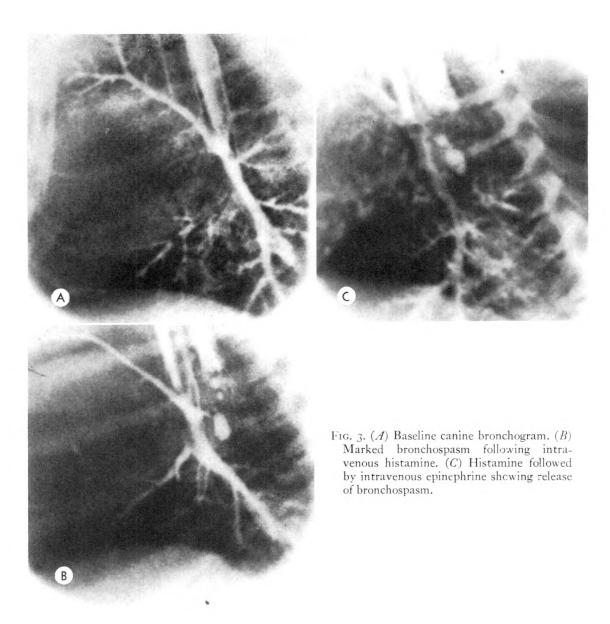
a time when they are most impressionable. The application of cinefluorography as a teaching instrument in undergraduate medical education has great possibilities and, therefore, should be seriously considered by educators. Although this effort has been

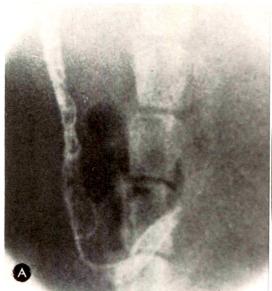
directed towards its use in medical pharmacology, this medium has the potential to be useful in the other basic sciences and in the clinical years as well.

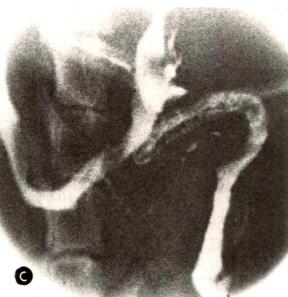
#### SUMMARY

A pilot study of the use of cinefluorography as a teaching instrument in the teaching of pharmacology in the medical curriculum is presented. Its usefulness in the study of drug actions makes it an extremely effective recording medium and

(Text continued on page 853)







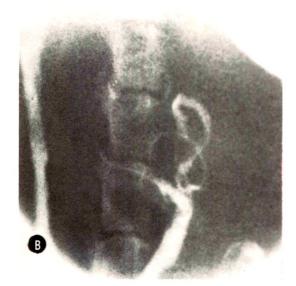
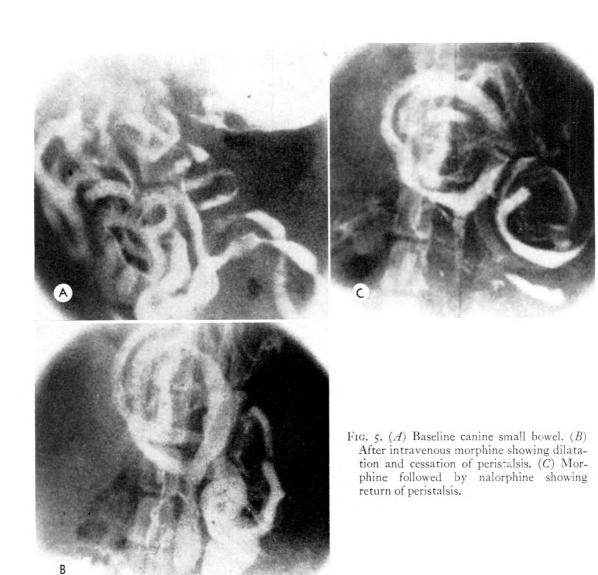
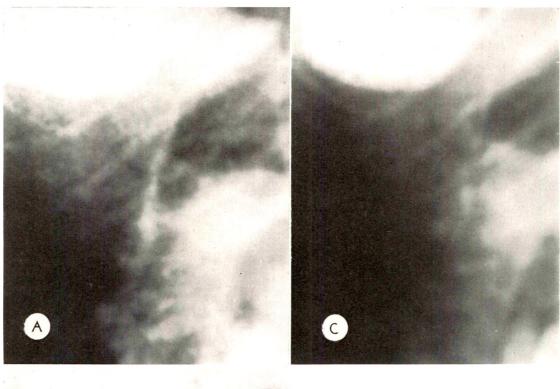


Fig. 4. (A) Baseline canine duodenum and small bowel. (B) After intravenous acetylcholine showing narrowing of the duodenum and increase in peristaltic contractions. (C) Acetylcholine followed by intravenous atropine showing dilatation of bowel and absence of peristalsis.





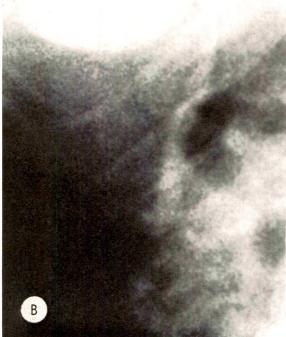
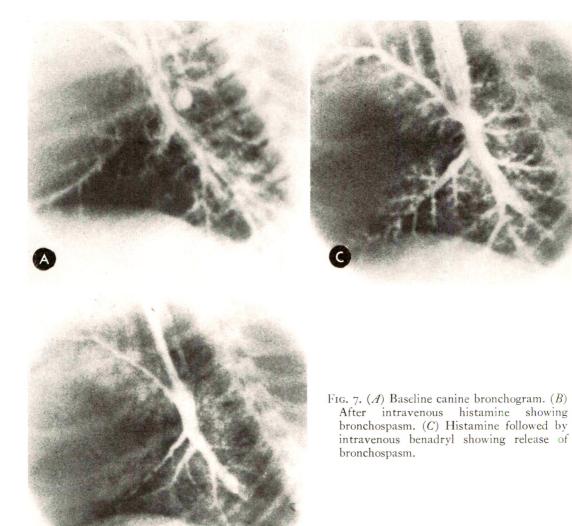
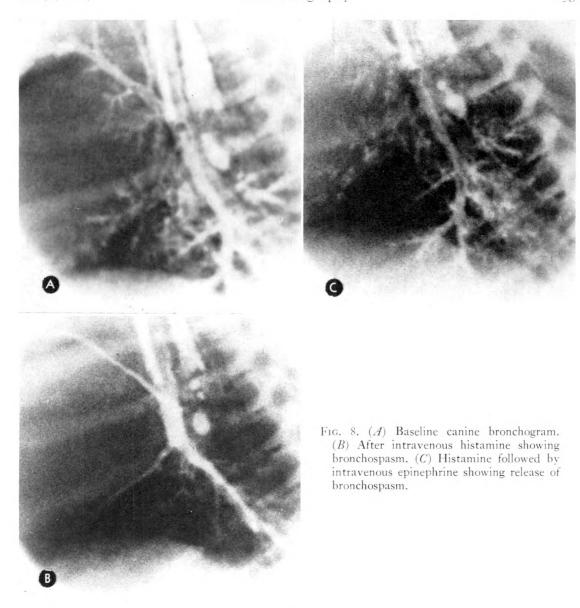


Fig. 6. (A) Baseline canine gallbladder and intravenous cholangiogram. (B) After intravenous morphine showing spasm of sphincter of Oddi and increased caliber of the common duct. (C) Morphine followed by intravenous nalorphine showing return of common duct to normal caliber.





provides a very dramatic method of illustrating these effects in experimental animals as well as living subjects. Such techniques can be utilized in bringing Radiology into the basic science years and indoctrinating the student early in his medical curriculum in the roentgen method.

T. E. Keats, M.D. Department of Radiology University of Virginia School of Medicine Charlottesville, Virginia

We are grateful for the help of Bill Lodwick, a student of University High School, Columbia, Missouri, for his assistance in this study.

# COMPUTER AUTOCODING, SELECTING AND CORRELATING OF RADIOLOGIC DIAGNOSTIC CASES\*

#### A PRELIMINARY REPORT

By HOWARD J. BARNHARD, M.D., and JOHN M. LONG, Ed.D. LITTLE ROCK, ARKANSAS

IT IS almost axiomatic that all diagnostic radiologists want to be able to retrieve pertinent cases but few like to code them. As a consequence, the dedicated ones force themselves to code but are far outnumbered by those who are casual. This broad range of effort frequently exists within a single department. Other problems exist: even the zealot may code the same case differently on separate occasions. Often only the most interesting diagnosis is coded and others are ignored because they have been overshadowed. Findings are usually not coded so they cannot be correlated with the diagnosis.

Thus, it is no surprise that few "trust" the code system. Private lists of cherished cases come into existence and are passed from hand to hand, while the cases carefully filed in the index system are ignored.

Dissatisfaction with existing code systems is also expressed by the frequency with which new ones appear. Unfortunately, all such efforts must inevitably be a compromise between the overly "simple" in which too many cases fall into each broad category and the overly "complex" system with a place for everything if one is strongly enough motivated to locate it.

We believe this problem can be solved with the assistance of the digital computer and will present our approach.

#### THE SOLUTION-AUTOCODING\*

Our solution to this indexing dilemma is to have the words in the report serve as the triggering mechanism of a computerized

\* Autocoding as used herein does not refer to Autocoder, a synthetic language used in programming computers.

coding process, *i.e.*, autocoding. As will be shown, this approach not only relieves the physician of an odious responsibility but has potential far beyond that of existing code systems.

The radiologic diagnostic report can be easily entered into the computer since there are special typewriters which produce the standard report and simultaneously punch either paper tape or cards in machine "readable" form. As this information is fed into the computer we wish to store only the pertinent or key words. This goal could be simply accomplished by giving the computer a list of key words and it would discard all other words. But among these rejected words would be some key words inadvertently misspelled and an occasional new word which should be added to the key word list. Thus there is need for a discara word list which, when used in conjunction with the key word list, will eliminate all but the misspelled and new words. Accordingly each word is evaluated and subject to three possible fates (Fig. 1):

- (a) If a word matches with a discard word it is rejected.
- (b) If it cannot be found in either the discard or the key word list, it is placed with information identifying its source in a special list of unknown words. This list is evaluated periodically. Misspelled words are corrected and re-entered into the computer. The remaining unknown words are classified as key and discard so that subsequently they will be "recognized" by the computer and handled automatically. In this manner new key words are picked up and there is no transition period during which cases are lost.

<sup>\*</sup> Presented at the Thirteenth Annual Meeting of the Association of University Radiologists, Seattle, Washington, May 13-15, 1965.

Assistance was provided for this research by the University of Arkansas Medical Center Computing Facility which is supported by NIH Grant GM 09839-02.

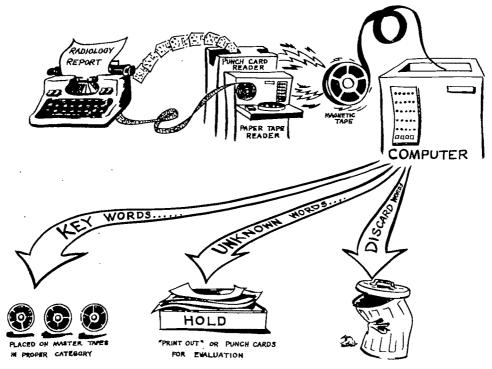


FIG. 1. The words of the radiology report are typed (upper left) and simultaneously punched on paper tape or cards in machine readable form. Following transfer to magnetic tape the computer compares the words of the report with its "dictionary" and treats them as key, discard or unknown words (see text).

(c) Most important is the fate of a word in the report which is found on the key word list. Each key word on the list has a file area on magnetic tape. When a key word meets all criteria as described later, that case is listed in the appropriate key word file. The cases are placed in numerical order according to the patient's identification number.

When a new case is added to tape, room must be made for it in the midst of other information. This is done by reprinting all data on a new tape, the new case pushing ahead all information which was beyond the point of its insertion. As the system grows beyond one tape, it becomes too time consuming to add to the various key word files scattered amongst all the master tapes each time new records are added. Therefore an "intermediate" magnetic tape is created in exactly the same manner as the very first tape and the information is merged onto the master tapes when the intermediate is full. When a search for cases is in progress,

the intermediate tape is scanned along with those master tapes which contain the key word files under consideration.

#### THE KEY WORD

The key word list is compiled by a combination of methods. The most direct route is to select words from existing index systems.<sup>1,2</sup> Next, the computer makes a word list from a cross section of radiologic reports. Those words, preselected from existing indices, are marked for easy identification. The frequency with which each word occurs is also shown. The frequency count is of value since, in general, the more often a word is used, the less its retrieval value. The words may be listed alphabetically or in order of frequency, or both.

From this list, key words are selected on the basis of their anatomic, etiologic, or pathologic information value. Preselected key words are re-evaluated and new key words are added. Synonyms are identified so they will be treated by the computer as though they were the same word and so all cases would be filed together. Those words which remain constitute the discard word list. As mentioned earlier, additions are made periodically to both key and discard word lists from evaluation of the unknown words which the computer has failed to find on either list.

There are three categories of key words based on their dependence on one another: (a) "anatomic" terms such as bronchus, (b) "pathologic" or "etiologic" entities such as fracture or tuberculosis, and (c) independent terms in which both the anatomy and pathology-etiology are indicated or understood as in nephrocalcinosis, and tetralogy of Fallot. Each key word will have a category designator. "Independent" key words are meaningful by themselves. Anatomy and pathology-etiology key words have little value taken separately and are, therefore, acceptable only if both categories exist within the same sentence or clause.

Anatomy key words will be grouped in a hierarchy so that the largest appropriate group may be sought, thus avoiding the listing of all the smaller areas involved. For example, the entire skeletal system or the spine, or the cervical region alone might be requested for pairing with some pathologyetiology category key word.

A similar approach will be used with pathology-etiology terms so that, for example, all infections may be sought or only those due to tuberculosis.

It may prove time saving to list the incorrect spelling of words that are frequently so spelled. By this means, misspelled key words would be treated as synonyms. Discard words would be dropped as usual. This practice would save the trouble of evaluating misspelled words when they appear on the unknown list.

Where terminology changes, the entire listing under a key word file can be transferred to a new category or only the appropriate cases could be moved. As an example of the latter situation, all "cholesteatomas" in the "calvarium" could be placed in the

new category of "epidermoidoma" leaving behind those cholesteatomas in the mastoid region still correctly classified.

Longest string concept. It would be possible to list all key words in separate files but adjacent related words are more easily retrieved if kept together. For this purpose the key word may actually consist of a "string" of words. It works thusly: The computer comes upon the word "inferior" in a report. This word is in the computer vocabulary but so are the key word strings "inferior accessory lobe" and "inferior vena cava." So the next words in the report are scanned and the longest possible string of words is matched.

Patient identification number is the means by which the case is identified in the key word file. We use the hospital unit number for our radiology patients. Any number system is easily used as long as it is consistent. Should the identification number change on each visit or each year a complexity is introduced but it is not insurmountable. If the computer is aware of both the old and new numbers, it can make appropriate changes before printing the lists of cases.

Key word qualifiers are information which is stored with the patient identification number in the key word files (Table 1). The qualifiers contain pertinent information which could be stored elsewhere but save much computer time if included in the basic file. Qualifiers are of 2 types: (a) simple qualifiers such as date of examination, race, sex, and age (determined by the computer which subtracts the information given of birth date from examination date),

Table I
KEY WORD IDENTIFICATION

Patient Number	Take Classes		Sex	Age	Race	
03-47-53	07-12-63	09	M	22	w	

A key word is identified in this fashion and placed in numerical order by patient number in the key word file. "Date" refers to date of examination. Additional qualifiers such as proof of positivity can be added to this identification as they are developed.

and (b) syntactic qualifiers, a much more complex category since analysis of the sentence is required. These are discussed in the following section.

#### SYNTACTIC KEY WORD QUALIFIERS

Whereas many languages have an orderliness about them that permits easy identification of the various elements in the sentence, English is a relatively helterskelter affair. It is thus difficult to establish rules for the analysis of the way in which words are put together in the sentence. The syntactic qualifiers which follow vary considerably in the linguistic complexity required to make them available for machine processing.

Sentence (clause) location. The date serves to pinpoint a specific examination, provided multiple reports occurring on the same day are identified. The date plus the sentence number within the report allows key words which occur close together to be related to one another. Otherwise "osteomyelitis" and "tibia" may seem to be related when actually "fracture of the tibia" and "osteomyelitis of the fibula" were described in the same report. Further division of sentences into clauses may be used if it is found necessary to tie key words together even more closely.

There is a potential trap in this approach in that, even though near each other, key words may not interrelate the same way each time. The familiar example is that a "blind venetian" is not the same as a "venetian blind." While specific instances can be managed, sophistication necessary to handle this problem on a broad front is not yet available. However, we expect these instances to be few in number. Some errors will be averted by the longest string approach. At worst, too many cases would be filed rather than cases lost. The improperly classified cases would be obvious if the roentgenograms or reports were reviewed.

Negation is a syntactic method for preventing the storage of key words not appropriate for coding. For example: There is no evidence of "hiatal hernia" contains an

obvious key word string but it also contains the negative word "no." From this we might formulate a rule that-Any key word which follows "no" should be ignored. But what if the sentence reads: There is no evidence of "hiatal hernia" but achalasia is present? Then the rule must be modified to read—Any key word which follows "no" should be ignored unless the key word follows a connector such as "but," "however," "although," etc.

Now re-form the sentence into: Despite no evidence of "hiatal hernia," esophagitis is present, and the "comma" must be considered one of the "connectors" in the preceding rule. But this modification fails in the sentence: Despite no evidence of "hiatal hernia," "varices" or "malignancy," "esophagitis" is present.

These difficulties in linguistic analysis do not mean that a hopeless situation exists, rather it requires that a decision be reached. The matter to be weighed is the filing of too many cases which occurs if no negation is used, versus the loss of cases caused by "rules" which occasionally negate key words which should be kept. These factors can be evaluated by running a group of reports through the computer to capture and evaluate sentences which contain negating words. Our results thus far indicate that sentences in radiologic reports tend to be fairly simple and the "negation rules" work very efficiently.

Other examples of negating words are: Duodenal ulcer is "not" present. There is diverticulosis "without" evi-

dence of diverticulitis.

The calvarium is "normal."

"Neither" fracture "nor" dislocation is

Evidence of gastric neoplasm is "lacking."

In practice, the computer first scans a sentence looking for negating words. When it finds one, it shifts into a sub-routine where the rules are available. That portion of a sentence in which key words are to be dropped is simply ignored except for finding

Table II
POSITIVITY HIERARCHY

I.	definite pathologic,	chemical, serologic, etc.,
II.	definitely	undoubtedly
	positively	pathognomonic
	unquestionably	classical
	an "unqualified st roentgenologic pro	ratement" also indicates of
III.	probable	thought to represent
	almost certainly	felt to represent
	most likely	consistent with the diagnosis of
	strongly suggest	
IV.	possibly	could conceivably be
	possibilities include	remote chance
	•	remote possibility
	should also be con- sidered	cannot be ruled out
	occasionally due to	unlikely
	rarely	may or may not

words such as connectors which indicate a change in sentence "direction."

Degree of positivity hierarchy is shown in Table II. With a positivity indicator, case selection may be limited to certain categories of proof or the cases selected might be listed in order of decreasing likelihood of the diagnosis being correct.

Category I being of proven cases would ordinarily be introduced into the computer when the information became available. If it were a proven case at the time it was being reported, the computer could be notified by use of the word "proven" or some arbitrary symbol such as an asterisk.

Categories II—IV are degrees of radiologic proof based on a distribution of word "strength" into three groups in decreasing order. Category IV may be considered eventually so weak in proof as to make it negate the filing of the key word to which it refers. The linguistic problem in Categories II—IV is somewhat more formidable than that involved in negation. There are a large number of potential word modifiers to be "discovered." Assessing which key words are being affected may also be more difficult than in negation.

It also would be possible to modify the

degree of positivity relative to the expertness of the reporter. Thus, residents could be identified by years of training with staff in a higher category. The computer would obtain this fact by noting the names of the reporting radiologists.

Size or degree are syntactic qualifiers. Size may be indicated as "small," "normal" or "large." If an actual dimension is given it could be recorded in numerical form or matched by the computer against a table of accepted values and recorded as "small", "normal", or "large." Degree may be indicated by terms such as "slight," "moderate", or "marked."

Side (left, right or both) are qualifiers which may have limited value where processes such as "fractures" are involved. However, the side involved may be more significant in evaluating "pleural effusions," for example, in which one side appears to be more commonly involved than the other in certain conditions. But even where no such tendency has been noted, it may be found to exist when a study is made.

#### CASE SELECTION

If the cases desired are complete under a single key word file such as "pneumothorax," that file may simply be printed out. By use of the qualifiers which follow each patient number, it would be possible to print the list of males separate from the females, Caucasians apart from Negroes, or to arrange the list in order of increasing age. An extension of this process is to select only cases, for example, of Negro males between the ages of 20 and 30. We could also obtain a frequency distribution according to age, race and sex.

When one wishes cases of "osteomy-elitis" of the "humerus" and the key words are in different key word files, both files are run into the computer. Those cases which intersect with regard to patient number, date of examination and sentence (clause) number are printed out (Table III). As in the case of a single key word retrieval, it is possible to select or obtain frequency data on the basis of the qualifiers.

Table III
INTERSECTION

Key Word "A"	Key Word "B"
034753, 071263, 09M22W ←	012469, 111556, 02F10C
934890, 010665, 21M60W 091106, 121652, 01F20C	034753, 071263, 09M22W 100090, 100559, 10M39W
121212, 101560, 06F41C -	→ 121212, 102060, 09F41C
150923, 073057, 15M32W	131517, 091656, 05F83C

Cases as they would appear under key word files "A" and "B" (see Table 1 for an explanation of the numbers and letters). The upper double ended arrow demonstrates intersection as it occurs in case selection where key words "A" and "B" are interrelated; note that the identification matches for patient number, date of examination and clause. The lower double ended arrow shows case correlation and the intersection here is one of case number and a time span within the acceptable limit.

By use of the degree of positivity qualifier, the cases selected might be only those which are proven, or they could be arranged in order of decreasing likelihood of the diagnosis being correct.

The computer can also arrange cases according to an external file order. This approach eases the problem of manually extracting patient material not on magnetic tape, such as roentgenograms and pathology slides. File order can vary from simple ascending numerical order to one based on the terminal digit system. Transposing from one number system to another can also be done.

The mechanics of retrieving requires that the proper master tapes be placed in position. This presents no problem since a record of the location of the various key word files is made at the time the intermediate tape is merged onto the master tapes.

#### CORRELATION STUDIES

Case correlation is essentially an extension of the process of case selection. If one wishes to determine the relationship between "lymphoma of the stomach" and "enlargement of the spleen," the two are intersected with regard to patient number and time span (Table III). By "time span" we mean the maximal spread of time over which the interrelationship would likely be significant. This time span would differ depending on the matter under consideration. Thus for "gastric lymphoma" and

"splenomegaly" it might be 6 months, but only 2 weeks in correlating "pneumothorax" with "rib fractures."

Within the past several years, there have been significant contributions made in the mathematical aspects of medical diagnosis.<sup>5</sup> This approach is based on evaluating the probabilities of certain signs and symptoms being present in a given diagnosis. In the area of congenital heart disease, the computer has equaled the performance of experienced physicians.<sup>4,6</sup> As more cases are analyzed the computer in a sense gains experience and it is likely that in time it will exceed the best that man can do.\* By a similar approach, we plan to correlate roentgenologic findings with proven diagnoses.

But the greatest gain will not be derived from placing every case in the computer for analysis. Rather, it will be the development of significant information which will help in everyday diagnosis. If, for example, it is found that of 10 potential findings in a given disease process 4 are most significant, these 4 findings can be particularly sought and given greater weight when they occur.

#### PROGRAMS CREATED

The development of programs, so-called "software," tcan be a very time consuming

ability to handle figures "in his head."

† "Hardware" refers to the mechanical and electronic components.

<sup>\*</sup>It is probably well to remind ourselves here that the computer is a product of man's creativity and it extends man's mind in much the same way as the simple desk calculator exceeds man's shill to to handle foures "in his head."

and costly procedure. The approach used may serve as a stepping stone to more advanced projects but the passing on of these programs to other users represents the most concrete scientific contribution.

We have had to develop many programs. Several are small "oneshot" programs written to test for certain situations which occur in diagnostic reports, to create test records for programs and to test the time required to execute various repetitive computer operations in order to get the optimum program. More complex programs include a set designed to capture, code and store the records.

The capture, code and store programs for this project have the ability to scan a combination of fixed and variable format records, selecting and processing vital data. The patient number, race, sex, date of birth and date of examination are the only fields that are fixed in either position or length. The rest of the record is completely variable in format. At the present time, the dictionary must contain each variation of each word used in the records processed (see item 2 in the paragraph below). The dictionary list is updated by a separate program prior to the capture run. Each word in each record is compared against the dictionary. If the word is not in the dictionary list, it is printed for visual checking. If it is in the list and is a key word, a record is written containing the code, fixed field data, and the number of the sentence and sentence segment in which the word was found in the record. These records are sorted and merged with previously captured records.

Routines have been tested but not added to the master programs which: (1) will treat certain word chains as one word, (2) will handle "s" and "ed" suffixes so that only root words need be stored, (3) will consider negating words so that key words without significance will be ignored, and (4) will indicate the words "left" and "right" in the stored record where applicable. Some research has been done toward indicating the degree of positivity of key words, but this routine is still developmental.

The selection-correlation program, using one-card-per-request input, will print the patient number of all records containing a selected key word, any two key words, any three key words, designated race, designated sex, patients below a maximum age, above a minimum age, or within a selected age span. Any combination of the above may also be printed. For example, a card could ask for records of all white males between 26 and 32 years old with "fracture" and "femur" occurring in the same record, the same sentence, or sentence segment, depending on console switch settings.

Routines which have been tested but not added will: (I) select on "left" or "right," (2) select only records in which the words are equal to or above a given positivity value, (3) exclude records containing specified undesired key words, and (4) select fields or subfields, such as "gastro-intestinal" or "esophagus."

The programs are designed for a relatively small computer, the IBM 1401, with 16 K storage and six tape units. We believe the approach could be accomplished with half the storage and tape units.

#### DISCUSSION

Much of the material has already been discussed as the various elements of this data system were presented. Here, we will relate some of the reasons for our preliminary decisions, current analysis and prognostications.

There is a recent report of a pioneering effort which effectively used the computer for coding neuroradiologic procedures. Our reasons for not pursuing a similar course should help explain the logic of the approach we have chosen. A primary point is that they directed their efforts to a limited field of radiology, while we set out to meet the broad needs of diagnostic radiology and perhaps establish the basis of a method to use throughout clinical medicine. With these broader goals in mind, we felt we had

to bypass the stage of development which they have reported.

In their system the neuroradiologic report must be dictated according to a fairly rigid format, then via punched tape the entire report is placed on magnetic tape. Though a rigid format for the report is the simplest approach, it in effect fits man to the machine rather than the machine to man. Any time man is required to overly adapt to a machine he must be extraordinarily motivated or he will avoid its use. Additionally, the many types of diagnostic radiology examinations would require different formats.

Their storage of the complete radiologic report on magnetic tape requires that all tapes can be searched each time information is desired. As more reports are added this approach becomes increasingly inefficient. Also, syntactic analysis must eventually be done in order to skim the cream from the report. It seems more efficient as a preliminary step to analyze the record and store only the pertinent information rather than analyze each record with every search. This premise is based on the assumption that the major objective is selection and correlation of specific cases rather than recovery of the report itself. Even though the report is not on tape, retrieval of the case number and date of examination leads one to the roentgenograms and the reports filed in the same folder. If there is a continuing need for the reports it would probably be more economical to store the reports in numerical order on a separate set of tapes. In the future the entire patient record will likely be kept in some mass storage device similar to magnetic tape but more accessible. Then, it will be possible to call forth the radiologic report if such were desirable.

As we established the fundamental logic of the system, it became obvious that an understanding of language would be required to put it to fullest use. We hoped that efforts of others in language translation would help us. We were to be disappointed. Despite the fact that languages

such as Russian and German apparently have more orderly word interrelationships and exactness of meaning than English, machine translation continues to be unsatisfactory. However, whereas language translations must develop full meaning, our immediate needs are less stringent. We, therefore, embarked on a program of working out negation rules and have begun to apply them to several thousand reports. Preliminary results indicate that our simple negation rules are remarkably efficient, that is, few key words are lost and few key words are retained which should have been dropped. Though not perfect, this solution seems infinitely more desirable than the excess of key words which would result if the negation routines were not used.

Our work with proof of positivity has been rudimentary other than to permit separate entry of the information when a case is proven (Category I proof in the positivity hierarchy). Further development would involve complex handling of language. Since this part is not essential to the success of the basic system, we have not developed it further. In the future we will try to overcome the problems since this nicety has great promise as a time saver and would be of value in correlation studies.

The computer-oriented system we have devised is a radical departure from conventional coding approaches. It is still in the developmental phase and will undoubtedly undergo changes based on increasing experience in the use of computers and the availability of new types of equipment. What then are the current and future prospects of this method?

As indicated, the system is deficient in its syntactic approach because the state of the art is not further developed along these lines. Thus, one must at present be prepared to accept a small error level in key word storage and a lack of finesse which will improve as the method develops further. Despite these limitations, we believe that the over-all convenience, effectiveness,

and flexibility of the system as already developed far exceed those of any existing system.

Cost is inevitably a consideration. Unfortunately, we cannot estimate cost accurately. Much of the expense of development is in software (programs) which could be adapted to other computers with relatively minor modifications. The cost of running the system depends upon many variables. Basically, the larger computer is more efficient and thereby lowers the cost of the operation. The use of a very large computer on a time sharing\* basis would result in the least cost. Against whatever cost eventuates must be balanced the radiologist's time and that of the secretaries and clerks who maintain existing code systems. Beyond that, it is impossible to assign a meaningful dollar value to the advantages which this system offers over conventional diagnostic coding systems.

What of the future? Input of data will be further simplified by typewriters which simultaneously place the information directly on magnetic tape. The typewriter may even place the report in the computer's memory where it will not only be available for autocoding but for transfer to the patient's chart which is also stored in the memory system. This latter feature anticipates major developments in inexpensive mass storage units with the information readily accessible and not on magnetic tapes which have to be placed by hand on the machine. Undoubtedly sophistication in English language handling will improve. Words in the report will become increasingly meaningful to the computer so that analysis may be further refined. It will become less expensive to use computers. Computers may become available as a utility like electricity so that one plugs into the line on a continuous basis but pays only for the time used.

The crux of any data system is that one be able to find the pieces and combinations of pieces of information in a reasonable time and at reasonable cost with maximum efficiency; i.e., maximum completeness (data wanted), minimum redundancy (repetitious data) and minimum noise (unwanted data). We are convinced that the computer offers the means of approaching an ideal system. No claim is made that we have but probed the surface. Whatever the reader may feel our data system offers him, it should not be long before increasing convenience coupled with decreasing cost make a computer-oriented approach as essential for diagnostic indexing as the automatic roentgen-ray film processor has become in its area.

#### SUMMARY

Without a specific plan for indexing case material, it cannot be retrieved. The large number of code systems which radiologists have devised for their diagnostic cases attests to both the need and the chronic dissatisfaction with existing codes. Now the high-speed digital computer shows great promise of aid in this problem and of opening new vistas in case correlation.

Herein is described a system which will permit the pertinent words in the radiology diagnostic report to form the basis for retrieval of the case. With the use of a special typewriter, the regular report is typed simultaneously with punched paper tape which is then fed into the computer. The computer analyzes each word and wordseries and compares them with two special word lists. Key words are retained and filed with appropriate identifying data. Discard words are lost and unknown words (not on either word list) are printed out for evaluation. Retrieval and correlation are possible within a wide variety of possibilities, including such additional identifying data as race, sex, age, and degree of positivity.

Howard J. Barnhard, M.D. Department of Radiology University of Arkansas Medical Center Little Rock, Arkansas

<sup>\*</sup> Whereby several projects are handled simultaneously.

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# THE VALUE OF SERIAL SERUM ELECTROPHORETIC STUDIES FOR PROGNOSIS IN PATIENTS IRRADIATED FOR CARCINOMA OF THE CERVIX\*

By EDWIN J. LIEBNER, M.D., GERTRUDE ASROW, B.S., and GERALD D. VERMEULEN, M.D. CHICAGO, ILLINOIS

MUCH has been written on hematopoi-etic effects following irradiation;<sup>5,11,12</sup> however, many of these studies are concerned with acute syndromes and total body irradiation.8,9 More recently, the effect of total body irradiation on immunity has received considerable attention, particularly with reference to tissue transplantation.4,16,17 During roentgen therapy, observations have also been made on the peripheral blood of patients. 10,18,14 The subtle physiologic changes occurring as a result of total body irradiation are difficult to evaluate. When limited volumes of tissue are treated, excepting the thymus, liver and spleen, physiologic changes remote from the treated region have not been reported with any reliability.

The development of electrophoretic analysis of serum proteins has made possible the study of protein changes in animals receiving total body irradiation. Human studies have been focused on the alteration of serum protein fraction in patients with cancer in an effort to find distinctive patterns. Only a few studies are available concerning the protein patterns in cancer patients who have received localized radiation therapy. Previous studies have included a variety of neoplasms, and little attempt has been made to secure controlled studies.

This investigation was undertaken: (1) to determine if alterations in serum protein fractions could be observed in patients responding to irradiation and those failing

to do so; and (2) to determine whether a serum protein electrophoretic pattern could be found as an indicator of prognosis or radiosensitivity.

A single neoplasm, carcinoma of the cervix, was selected for study in order to define shifts in serum protein fractions, either intrinsic (due to patient's condition) or extrinsic (due to radiation and/or intercurrent disease which may occur before, during, and after radiation therapy). Also, a single type of neoplasm was chosen to preclude variations in the protein fractions due to other kinds of neoplasms and organ involvements, or to dosage and duration of irradiation.

#### METHODS

The patients selected covered a relatively narrow age span and had in the management of their malignancy a fairly uniform volume of pelvic tissue treated to the same dose level in the same time interval.

Normal females who were seen at the University Health Service Employment Office between the ages of 25 and 55 were used as controls. A blood sample was obtained from each of 39 women and their serum protein electrophoretic analyses were made.

During the period of September, 1959 through September, 1962, all consecutive patients with carcinoma of the cervix who were accepted for radiation therapy were included in the study. A blood sample was obtained prior to any treatment, another

<sup>\*</sup> Presented at the Thirteenth Annual Meeting of the Association of University Radiologists, Seattle, Washington, May 13-15, 1965. From the Departments of Radiology and Pediatrics, College of Medicine, University of Illinois, Chicago, Illinois. Study aided by a grant from the Graduate College, University of Illinois.

later during the treatment period, and a third sample in the follow-up period anywhere from 3 months to I year after treatment. A few patients had more than 3 determinations, but in the final analysis only the data from the pre- and post-treatment serum electrophoretic pattern were considered for statistical analysis.

Management of these patients did not deviate in any way from our regular method of treating carcinoma of the cervix. Generally, radium insertion was made first. Then external radiation therapy was given; this was interrupted briefly to do the second radium insertion about 2 weeks after the first. The intracavitary radium consisted of a separate tandem containing 27-35 mg. and Manchester ovoids having a combined total of 36-48 mg. of radium, generally applied in 72 and 48 hour courses. The factors of the external radiation therapv used at that period were: 300 kv.; half value layer of 4 mm. Cu; 19.5 ma.; 50 cm. treatment distance; anterior and posterior pelvic portals of two 8 × 15 cm. fields, separated by a 4 cm. lead strip in the midline. The anterior and posterior portals were treated alternately with a daily skin dose of 300 rads to each 8×15 cm. field. The treatments were given 5 times a week for an average total time of 5 weeks. The skin reaction was usually carried to moist desquamation. A 3,000 rad tumor dose to the midplane of the lateral pelvis was delivered by the external irradiation. The radium applications usually contributed 6,000 rads to Point A and 1,500 rads to Point B.

Serum protein fractionation was performed by using the Spinco Model RB Paper Electrophoresis System, consisting of the Durrum-type electrophoresis cell, a regulated power supply, and a calibrated recording densitometer with the automatic integrator. The technique consisted essentially of moistening 8 strips of filter paper with Veronal buffer, pH 8.6, ionic strength 0.075, and arranged on a hinged rack in an inverted "V." The ends of the paper strips connected through paper wicks and electrolyte reservoirs to positive and negative

electrodes. After moisture equilibrium in the cell had been reached, an accurately measured amount of the sample was applied as a narrow stripe across the center of each strip at the top of the inverted "V."

After the sample was fractionated in the electrical field created by a regulated power supply, the hinged rack was opened and the set of paper strips was oven-dried to fix the pattern. The bands were made visible by staining with a bromphenol blue dye. Concentrations were then determined on the basis of light absorption of the stain by scanning in the Analytrol densitometer. From the data thus obtained, the relative amounts of each of the individual components were determined. All specimens were run in duplicate.

Serum total proteins were determined according to an adaptation of the ultramicro method of Goa<sup>6</sup> which is based on the Biuret reaction. The technique consisted of adding 10 µl. of serum to 4 ml. Biuret reagent, prepared by mixing 1 part of copper solution (Benedict reagent) to 20 parts of 3 per cent NaOH reference. The outer diameter readings of the blanks were subtracted from the sample, which corrects for hemolyzed, icteric, or chylous samples.

A calibration curve was prepared from a standard protein nitrogen solution\* ranging from .06 mg. per sample protein nitrogen to 0.2 mg. per sample protein nitrogen. The standards and blanks were carried through in the same manner as the unknown. All samples were read in a Beckman Du Spectrophotometer at a wave length of 340 mu.

#### RESULTS

Although initially there were 48 patients who had pre-treatment studies, only 22 women had the required follow-up samples later in the treatment and post-treatment follow-up periods. The remainder was not included for the following reasons: (I) treatment was incomplete, (2) patient failed to return for follow-up visits, and (3) the blood specimen itself was contami-

<sup>\*</sup> Armour Pharmaceutical Company Protein Standard crystalline bovine albumin.

nated, broken or improperly refrigerated, while waiting for the serum determination.

After a 2 year period of observation, the 22 patients who had pre-treatment and post-treatment determination were divided into 2 groups. One group consisted of 9 patients who had died or had far advanced disease. The second group consisted of 13 patients whose disease had been arrested during the same interval.

Utilizing these 2 groups, a statistical analysis was made. The mean differences (pre-treatment minus post-treatment) and t-statistics (mean difference divided by standard error of difference) were calculated for each protein component of the serum (absolute concentration). None of the t-tests was significant at the .10 probability level; i.e., no significant changes were demonstrated in the patients with either favorable or unfavorable outcome. However, in those with favorable outcome, there was a mean decrease in  $\alpha_2$  globulin which was nearly significant at the .10 probability level, while in those with the unfavorable outcome there was a mean increase in  $\alpha_2$  globulin which was nearly significant at the .10 level. The difference between patients showing good and those showing poor outcome in the change in  $\alpha_2$ globulin was significant at the .05 level.

The statistical technique of discriminant analysis was used to see to what extent the absolute concentrations of the protein components could be used to distinguish between the normals and the cancer patients (using pre-treatment values). The over-all discrimination was very highly significant (p < .0005). Twenty-eight of 33 normals were classified correctly, and 27 of 36 cancer patients. The two important discriminating factors were albumin and  $\gamma$ globulin. Pre-treatment values were next used to discriminate between patients with good and poor outcome. The discrimination was not statistically significant, only 16 of 22 good and 10 of 14 poor outcomes being classified correctly.

The next attempt was to discriminate between patients with good and poor outcome on the basis of both pre- and post-treatment values. The discrimination was significant at the .05 probability level. Twelve of 13 good and 7 of 9 poor outcomes were classified correctly. Most of the discrimination was achieved by the factors: post-treatment  $\alpha_2$  globulin, pre-treatment  $\alpha_2$  globulin, and pre-treatment albumin.

#### DISCUSSION

Ciampelli<sup>2</sup> studied 81 patients with malignant neoplasms for electrophoretic variation as a biologic indicator of radiosensitivity. Only 44 had localized malignant neoplasms that were treated primarily by roentgen therapy. In 33 of these patients, the neoplasm responded to treatment and an increase of  $\gamma$  globulin from 20 to 50 per cent above the initial value occurred, to which it returned after completion of treatment. In the other group, no such increase in  $\gamma$  globulin was noted. The  $\alpha_1$  and  $\alpha_2$  globulin fractions showed a noticeable and constant rise in those cases failing to respond to irradiation.

Magno<sup>15</sup> performed electrophoretic serum protein determinations in 50 patients with lymphoblastoma and 54 patients with malignant epithelial tumors treated by radiotherapy. He concluded that no relationship between type of tumor and electrophoretic pattern occurred. In the lymphoblastoma patients, he frequently noted a reduction in the albumin and an increase in the  $\alpha_2$  and  $\gamma$  globulin fractions.

Ackerman and co-workers' preliminary report shows that in only 11 patients with various malignant diseases were the serum protein electrophoretic patterns studied prior to and after the maximum effect from radiation therapy to a localized region of the body. Ten patients showed a slight to moderate increase in  $\gamma$  globulin with no consistent change in the other protein fractions.

Graham<sup>8</sup> did protein electrophoretic analyses on the serum of 253 cancer patients. In active cancer patients (156), the albumin fractions were decreased with resulting increase in all other fractions.

These findings were absent or much less apparent in treated cases. One of his patients with a testicular seminoma and a large retroperitoneal metastatic mass had, after surgery and irradiation, a marked increase in the albumin fraction and a concomitant decrease in the  $\gamma$  globulin fraction. Graham found that an elevated  $\alpha_2$  globulin fraction was a sign of poor prognosis. He also found that the  $\beta_3$  globulin fraction was higher in the 50-59 age group due to the  $\beta$ -lipoprotein. This may be related to the higher incidence of vascular disease in this age group.

In our study, the patients with a favorable prognosis (Stage 1 or early Stage 11

lesions) showed a rise in the serum albumin and a fall in the  $\gamma$  globulin fraction, although in a few cases there was no appreciable change and the pre- and post-treatment values were maintained.

Table I shows the serum electrophoretic values in patients with advanced carcinoma of the cervix having a favorable result to date. Seven Stage III lesions and 2 late Stage II lesions are listed. Here again, the serum albumin fraction had maintained its level or had risen and the  $\gamma$  globulin fraction had maintained its pre-treatment value or had fallen slightly. In 2 patients (Patient 4 and 6) there were slight increases in the  $\gamma$  globulin fraction, with a fall in the

 $T_{\mathtt{ABLE}}\;I$  carcinoma of cervix patients with favorable results

Comments	Serum Electrophoretic Values (Per Cent)					Serum Total				
	Globulin					Protein (gm./1∞	Date	Stage	Patient Sta	
	γ	β	α <b>s</b>	an	Albumin	ml.)				
Radiation treatment 11-27-59	12.2	9.0	9.6	3.5	65.8	6.7	11-29-59	ІП	ı. E. B.	
1-13-60; 3-4-65 no evidence	11.2	9.1	5.9	3.5	71.2	6.8	1-6-60			
disease	9.7	9.8	5.4	2.0	73.I	7.32	2-17-60			
	9.2	8.1	5.4	2.9	74.1	7.15	10-19-60			
Radiation treatment 10-23-61	15.2	7.7	7.6	2.9	66.5	7.54	10-23-61	lIII	2. C. C.	
12-29-61; 2-17-65 no evidence	17.1	9.9	4.7	2.7	65.6	6.20	12-29-61	1 1	43 yr.	
disease	14.7	10.7	5.3	2.0	67.4	6.86	11-1-62			
Radiation treatment 5-11-61	11.1	9.7	6.2	2.4	70.4	6.24	5-11-61	III	3. W. H.	
6-19-61; 7-11-64 no evidence	11.6	9.4	6.8	2.5	69.7	6.41	6-22-61	1	25 yr.	
disease	11.2	8.3	9.8	3.4	67.4	6.30	11-24-61	i	• .	
Radiation treatment 10-2-61	15.4	9.8	10.7	4.9	59.3	6.53	10-2-61	ш	4. A. N.	
11-9-61; 11-6-64 no evidence	12.3	12.0	12.1	5.8	57.5	5.92	11-9-61		•	
disease	19.4	10.8	9.4	3.2	57.3	6.94	11-5-62			
Radiation treatment 11-16-61	14.9	8.7	8.4	4.5	63.6	6.78	1-4-62	III	5. I. H.	
1-4-62; 11-25-64 no evidence disease	11.4	10.3	9.9	4.6	64.0	7.20	6-13-62			
Radiation treatment 10-30-59	10.3	7.8	5.4	2.5	74.1	6.32	10-30-59	ını	6. D. H.	
12-10-59; Feb., 1965 no eviden	10.2	6.1	5.8	1.8	76.3	6.7	12-2-59			
of discase	14.3	11.2	7.7	4.7	62.3	6.69	10-14-60			
Radiation treatment 7-19-62	15.6	11.2	11.3	4.2	57.8	6.34	7-23-62	m	7. J. G.	
9-7-62; 10-9-64 no evidence disease	13.3	7.0	6.6	3.1	69.9	6.76	2-8-63			
Radiation treatment 10-12-61	13.7	7.4	8.0	3.6	67.3	6.90	10-12-61	п	8. W. M.	
11-17-61; 11-4-64 no evidence	12.1	8.7	7.3	3.9	68.I	6.70	11-17-61		29 yr.	
disease	17.0	7.4	11.2	2.0	66.3	7.82	11-5-62			
Radiation treatment 3-8-62	18.7	11.5	8.6	3.4	58.0	6.50	3-12-62	п	9. E. J.	
6-1-62; 11-18-64 no evidence	15.4	8.8	6.4	2.7	66.9	7.09	7-13-62		46 yr.	
disease	18.3	6.8	8.0	2.6	62.9	6.49	11-2-63			

Table II

CARCINOMA OF CERVIX PATIENTS WITH UNFAVORABLE RESULTS

		Stage Date	Serum Total Protein (gm./100 ml.)	Serum Electrophoretic Values (Per Cent)					
Patient :	Stage			Albumin	Globulin				Comments
					αι	ar <sub>1</sub>	β	γ	
1. A. L. 37 yr.	III	9-10-59 10-20-59 1-6-60 10-14-60	5 · 49 6 · 45 7 · 05 7 · 55	63.2 70.2 75.1 59.8	4·3 3.0 2.1 4.0	6.6 5.5 4.2 9.0	12.7 9.3 7.4 11.9	13.4 12.0 11.2 16.1	Radiation treatment 9-14-59 to 10-21-59; Papanicolaou amear on 10-14-60 reported Class 1; died 3-11-61 with metastases
2. R. S. 27 yr.	III	11-9-61 12-15-16 6-29-62	6.77 6.72 6.06	60.7 70.1 53.2	3.7 3.5 4.2	12.2 7-7 14.8	12.7 8.5 14.6	11.3 9.8 13.4	Radiation treatment 11-10-61 to 12-15-61; Aug., 1962 was well but within 1 yr. metastatic disease of right pelvic wall developed; died 1-13-64
3. E. S. 42 yr.	III	10-20-59 12-2-59 1-6-61	6.50 7.1 7.4	58.2 83.5 65.0	4.8 1.6 4.4	9.6 4.5 12.8	9.6 4·7 8.0	18.0 5.9 10.0	Radiation treatment 10-20-59 to 12-4-59; summer, 1960—Papa- nicolaou smear class 111, and right hydronephrosis; died 3-20-61
4. M. McM. 53 yr.	II	3-19-62 3-6-63	5.02 6.60	<b>54</b> .9 66.9	5.2 5.3	10.1 9·7	13.1 8.7	17.0 11.0	Radiation treatment 3-15-62 to 4-18-62; kiopsy 11-28-62—carcinoma of cervix; radiation treatment 12-28-62 to 1-21-63; died 9-14-63. Autopsy: rectovaginal fistula and hydronephrosis; no tumor found
5. J. C. 42 yr.	ш	1-21-61 6-20-62	5.99 6.52	60.5 39.0	3.6 7.1	11.1 18.4	12.1 14.0	12.8	Radiation treatment 1-13-61 to 3-9-61; diec 12-14-62. No autopsy
6. A. R. 46 yr.	III	5-4-61 12-8-61	6.21 6.85	69.3 54.7	2.6 4.2	5.6 7.7	9.I I4.0	13.5 19.6	Radiation treatment 5-5-61 to 7-14-61; died 3-15-62. No autopsy
7. C. T. 39 yr.	11	10-27-61 12-7-61 6-29-62	6.33 6.70 6.80	66.8 70.7 67.2	3·7 3.8 5.1	6.9 4·9 7·5	10.0 8.1 9.1	12.7 13.6 12.3	Radiation treatment 10-27-61 to 12-8-61; right leg lymphedema early in 1963; died 10-3-63
8. G. C. 45 yr.	II	11-29-59 1-6-60 12-7-60	7.60 7.22 7.96	61.4 66.0 66.4	3·4 2.6 1.7	8.1 6.8 6.1	8.8 9.0 9.1	18.1 15.7 16.8	Radiation treatment 12-29-59 to 1-14-60; July 1961—metastases to sacrum; died 2-2-62. No autopsy
9. V. G.	III	3-12-62 4-24-62 6-29-62	7.10 7.18 7.65	62.6 46.9 50.4	3·9 5·2 4·9	6.6 13.6 10.5	9.8 10.8 11.9	12.3 23.7 22.6	Radiation treatment 3-13-62 to 5-1-62; 2-17-65 progressive disease

albumin fraction. The patients have been followed 3 and 5 years, respectively, and no disease has been detected.

Table II shows the serum electrophoretic values in patients with advanced Stage III and II lesions who have had an unfavorable result due to the progressive course of the cancer. All have died except Patient 9, and she is reported as being in a terminal state. In this group of patients, as contrasted to those shown in Table I, the albumin values

had a tendency to fall with a concomitant rise in the  $\gamma$  globulin values and the  $\alpha_2$  fraction in most cases increased. Patient 1 is interesting in that a Papanicolaou smear on October 14, 1960 was reported as Class 1, while her serum electrophoretic values when compared with the previous values showed unfavorable result. The albumin value decreased, and the  $\alpha_2$  and  $\gamma$  globulin values increased. She complained of backache, but clinical and roentgenographic

study failed to demonstrate any positive findings. On March 11, 1961 she died of metastatic disease.

There are several additional comments that should be made in trying to interpret the results and/or significance of these findings. A single serum electrophoretic determination or changes in an individual fraction are not specific for cancer, since they may be seen in other types of disease (e.g., renal or hepatic), following surgery, or in the presence of fever or acute infection. One must also keep in mind that no pattern is fully diagnostic or specific of disease in itself. Various pathologic stimuli responsible for diverse disease states can affect the protein metabolic pool in a qualitatively similar manner.

However, serial electrophoretic determinations of the serum proteins of a group of patients with the same clinical stage of cancer of the cervix can be useful. These patients can be categorized according to their age group and screened for any other medical diseases or complicating factors. Since the volume and anatomic site of tissue irradiated are identical, a pre-treatment, late-treatment, and follow-up (6 month interval) electrophoretic determination can provide useful information on the efficacy of treatment.\*

#### SUMMARY AND CONCLUSIONS

Serial serum electrophoretic studies over an appropriate interval can show patterns concerning the general condition of the patient and the efficacy of the treatment. If the age group, clinical stage and site of the cancer and volume of tissue irradiated are controlled, these serum patterns can become more meaningful for prognosis.

In our clinical study with carcinoma of the cervix cases, it was found that the albumin and globulin values of these patients varied greatly from those of the normal controls. Pre-treatment findings were of little usefulness in discriminating between patients who obtained good and those who obtained poor results. By using both preand post-treatment values, the discrimination between those with good and those with poor results was significant (p=.05).

A comparison was made in the Stage III and late Stage II carcinoma of the cervix cases between those having a favorable response and those who died. In patients responding favorably to treatment, there was a mean decrease in  $\alpha_2$  globulin fraction, while in patients with unfavorable response, a mean increase in  $\alpha_2$  globulin fraction occurred (p=.10). The difference between patients with good and those with poor responses in the change in  $\alpha_2$  globulin fraction was significant at the .05 level. A rise in the albumin fraction and concomitant fall in the  $\gamma$  globulin fraction was considered a favorable pattern in the serial studies.

Edwin J. Liebner, M.D. 840 South Wood Street P. O. Box 6998 Chicago, Illinois 60680

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## TREATMENT FRACTIONATION IN NEW RADIATION THERAPY MODALITIES\*

By P. WOOTTON SEATTLE, WASHINGTON

WHEN investigating new therapy modalities, the logistics of patient manipulation, competition for or sporadic functioning of equipment may tempt the therapist to reduce the number of fractions of treatment employed.

When hyperbaric oxygen was first combined with radiation therapy at the Tumor Institute of the Swedish Hospital, fractionations similar to those described by Van den Brenk et al. 28.24 and by Churchill-Davidson were adopted—i.e., up to 6 fractions delivered in an over-all time of 3 weeks.

This scheme proved unsatisfactory to the therapist, particularly in treatment of carcinoma of the larynx. The value of fractionation in producing selective effects was recalled; and it was considered necessary to develop a fractionation scheme that was compatible not only with past experience of tumor lethal dose, but also experience of the tolerance of the supportive tissue.

It was attractive to contemplate the development of such schemes from basic radiobiologic data.

The meaning of *in vitro* cell survival curves for fractionated radiation therapy has been reviewed by several authors, perhaps most recently by Hendrickson.<sup>12</sup> Qualitatively, these studies would appear to indicate that provided the fractions of radiation are delivered sufficiently far apart for short-term recovery to take place but within an over-all period less than a cell cycle, then the net effect will be a function of the number of fractions into which the total dose is divided. This concept has some support from the work of Fowler, Morgan, Silvester, Bewley and

Turner on erythema in pigskin, with 5-21 fractions extended up to 28 days in experiments designed to clarify this point. De Moor, Durbach, Levin, and Cohen,6 in surveying data on carcinoma of the breast, suggest that the concept is valid for this disease. In general, it may be expected that if it is reasonably true for tissues responsive to challenge such as skin, it will be even more true of tissues incapable of homeostasis or rapid repair such as carcinoma or cartilage. The hypothesis was therefore made that provided the fractions are delivered more than 24 hours apart and in an over-all time of less than 28 days, then the radiation response will be a function of the number of fractions employed rather than the over-all time.

The next step was to derive a quantitative relationship between desired effect and the number of fractions employed.

The difficulty of reconciling quantitative calculations based on cell survival curves and the clinically observed tumor and normal tissue response as expressed in the isoeffect lines of the Strandquist<sup>22</sup> presentation has been reviewed by Fowler and Stern. These difficulties are not surprising, as (1) accurate experimental determination of the extrapolation number is difficult;21 (2) extrapolation numbers of 6 or more may arise from combinations of 2 and 3 hit number events; 11 (3) the shape of the in vitro survival curve may be modified by changes in the nutrient solution, even in the postradiation phase.1 This last factor may explain why similarities in radiation response of tumor cells and normal tissue in vitro have been reported by many workers, while different responses to fractiona-

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From the Division of Medical Radiation Physics, Department of Radiology, University of Washington School of Medicine, Seattle, Washington.

tion have been observed clinically where they may be expected to inhabit different nutritional environments.

In view of the uncertainties in the fundamental data, the restricted range of tissue for which the data are available, and the urgency of decision, it was decided to proceed from clinical data for clinical purposes. The literature was, therefore, surveyed for tolerance dose for skin with various fractionation regimens for 6 by 8 and 8 by 10 cm. fields. The data obtained were plotted in a modified Strandquist presentation that is, the total dose to produce the given effect was plotted against the number of fractions into which the dose was divided, on log-log paper. This study was repeated for oral mucosa, cartilage in the larynx, and the optimum—i.e., high control, low incidence of necrosis—doses for squamous cell carcinoma. The biophysical variables—that is, value of the roentgen, RBE, etc.—were avoided by normalizing the data at 4 fractions. In some cases, this allowed the data from a number of centers to be studied together.

If, then, a decision can be made about the acceptable absolute value of these parameters at a selected fraction number, the iso-effect line can be drawn in terms of absolute dose for all of the fractions by drawing a line parallel to the normalized data and passing through the absolute value at a fixed number of fractions. The sources of data and their manipulation were as follows.

# PARAMETERS SKIN

The data chosen for analysis were those of Paterson, <sup>19</sup> and Jolles and Mitchell, <sup>14</sup> whose definition of a tolerable reaction is that of a moist desquamatous erythema. These authors were chosen, as the quality of the radiation, field sizes and the number of fractions are clearly stated and are in the range of interest. These data normalized to 4 fractions are shown in Figure 1.

The absolute value of the skin tolerance for x-radiation, half value layer, 1.5 mm.

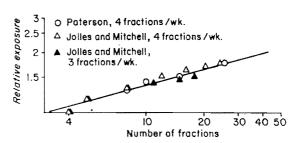


Fig. 1. Maximum dose to skin producing moist desquamation relative to 4 fractions as unit dose.

Cu through a 6 by 8 cm. field in 4 fractions, according to Paterson, is 3,300 r. The value according to Jolles' and Mitchell's published data is 3,900 r. However, Fowler and Stern<sup>8</sup> state that Jolles and Mitchell have reduced their values 10 per cent since 1951, yielding an absolute value of 3,500 r. The mean value gives 3,400 r for the skin tolerance for orthovoltage. According to the survey of Johns, the skin tolerance at supervoltage to the skin tolerance at orthovoltage is in the ratio of 1,000:740—that is, 1.35:1. Multiplying 3,400 by 1.35, a value of 4,600 r is obtained for supervoltage radiation.

The iso-effect line for supervoltage radiation is shown in Figure 2.

# MUCOSA

Mucosal tolerance was defined as a brisk, mucoidal, confluent mucositis. It was

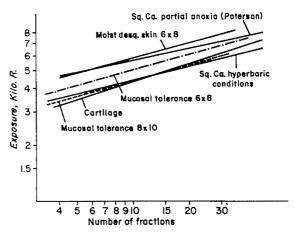


Fig. 2. Tolerance of normal tissues and minimum squamous cell carcinoma supervoltage therapy.

considered to be of the same order of magnitude as skin tolerance in the orthovoltage range; but in the supervoltage range, increased only by the change in RBE as reported by Kohn<sup>16</sup>—i.e., by I/.85=1.17:1. Therefore, the supervoltage tolerance of mucosa for 4 fractions may be set at 3,400 r for orthovoltage radiation and 3,980 r for supervoltage radiation for a 6×8 cm. field. The corresponding data for an 8×10 cm. field would be 2,950 r and 3,450. The iso-effect line for mucosal tolerance for supervoltage radiation is shown in Figure 2.

# CARTILAGE

The significance and frequency of sequestration of cartilage are a function of site, *i.e.*, whether the sequestration would have functional consequences and whether the site is subject to subsequent trauma. While cartilage may normally respond as a radiation-resistant tissue, compromised cartilage in the larynx would appear to be an exception. In clinical testing of new modalities, it is to be expected that the cases of carcinoma of the larynx are likely to be sufficiently advanced that the laryngeal cartilage is so compromised.

The data, reported by Gunderson, 10 regarding the incidence of cartilage necrosis in patients treated at the Fondation Curie, were replotted on log-log paper and a regression line was drawn between doses giving rise to necrosis and the next known dose in which necrosis did not occur (Fig.

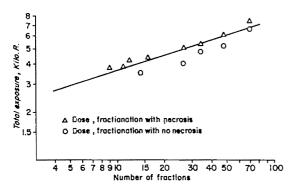


Fig. 3. Gunderson and Baclesse data on incidence of cartilage necrosis; carcinoma of larynx.

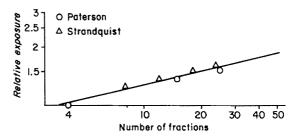


Fig. 4. Optimum dose for squamous cell carcinoma relative to 4 fractions as unit dose.

3). The absolute value of 2,800 r in 4 fractions at orthovoltage was adopted. As no correlation with other reports was attempted, the data were used directly for orthovoltage and modified for RBE by a factor of 1.17 for supervoltage. The isoeffect curve for cartilage for supervoltage radiation is also shown in Figure 2.

# SQUAMOUS CELL CARCINOMA

The data on squamous cell carcinoma offered by Paterson<sup>20</sup> and Strandquist<sup>22</sup> were normalized at 4 fractions (Fig. 4). The absolute value of minimum tumor dose was based on the data of Strandquist. The absolute data offered by Paterson are relevant to squamous cell carcinoma in general but include partially anoxic tumors. He states that his values are probably high. They are included for completeness in the data in Figure 2. It was considered that absolute data derived from small skin lesions would be more pertinent to the situation in hyperbaric oxygen radiation therapy. The values of dose for small lesions reported by Strandquist, 3,600 r, were obtained by a survey of results with equipment mostly operated at 100-120 kv. peak, 30 cm. focus skin distance, half value layer approximately 2 mm. Al. If the lesions were approximately 3 mm. in thickness, the *minimum* tumor dose was then of the order of  $3.1\infty$  r for orthovoltage. Modified for RBE by multiplying by a factor of 1.17, a value of 3,620 r is obtained for supervoltage radiation. These data are also presented in Figure 2. Similar data at 4 fractions were reported by Von Essen<sup>25</sup> from a survey of Tumor Institute patients.

# RESULTS

It was found that provided the number of fractions exceeded 4, the iso-effect curve became a straight line. This observation was applicable to all tissues studied. However, the slope of this line was different for different tissues. The relationship between the optimum dose for squamous cell carcinoma and the tolerance of supportive tissues was therefore a function of the number of fractions employed (Fig. 2).

The data may be represented by an equation of the form  $D_N = D_1 N^a$ , where  $D_N = \text{iso-effect dose in}$ 

N = fractions if N is greater than 4,

a = constant characteristic of the tissue system,

D<sub>1</sub>=the extrapolated iso-effect dose in one fraction.

This is a mathematical extrapolation and does not necessarily have biologic significance, as  $N_1$  is less than 4.

Least squares analysis of the data yields the following equations for orthovoltage radiation:

ceptable reactions, while 10 fractions would be required for an 8×10 cm. field. However, at least 15 fractions must be used before it becomes possible to adequately treat oxygenated squamous cell carcinoma situated near cartilage with ortho- or supervoltage radiation. The need for extended fractionation in any degree of anoxia can readily be appreciated from the Paterson squamous cell data. If fewer fractions are used, past experience would indicate that cartilage necrosis, and perhaps undue mucosal reaction, may be expected—irrespective of the use of hyperbaric oxygen. If adequate oxygenation of the tumors is not achieved, then more fractions are required in order to obtain tumor resolution without tissue damage. The use of few fractions reduces the margin for error in all cases; hence, more detailed dosimetry becomes mandatory for good control. The implications of the data presented in Figure 2 were checked against reports in the literature regarding (a) treatment of larynx, and (b) use of another

Squamous cell carcinoma (adequately oxygenated) Skin and mucosa	$D_N = 2,300 N^{.22}$
8×10 cm. field	$D_N = 2,000 N^{.28}$
6×8 cm. field	$D_N = 2,300 \ N^{.28}$
Cartilage (compromised)	$D_N = 1,760 \ N^{-32}$
And for supervoltage radiation:	
Squamous carcinoma (adequately oxygenated) Skin	$D_N = 2,690 N^{.22}$
8×10 cm. field	$D_N = 2,700 N^{.28}$
6×8 cm. field	$D_N = 3,120 N^{.28}$
Mucosa	
8×10 cm. field	$D_N = 2,340 N^{.28}$
6×8 cm. field	$D_N = 2,690 N^{.28}$
Cartilage	$D_N = 2,060 N.12$

It can be seen from these equations that for treatment with orthovoltage radiation of a well-oxygenated tumor with fields of the order of 6 cm. by 8 cm., I to 2 fractions would permit adequate tumor dosage under skin or mucosa but with marginally ac-

modality, electron beam therapy. Goodrich and Lenz<sup>9</sup> reported that in this series of carcinoma of the larynx, patients developing cartilage necrosis received an orthovoltage exposure of 6,000 r in 5

weeks. This would be  $6,\infty$ 0 r orthovoltage or  $7,\infty$ 0 r supervoltage in 25 fractions. Lederman<sup>16</sup> recommends the use of  $5,5\infty$  r radium gamma rays, in 30 fractions. Buschke and Vaeth<sup>2</sup> reported good mucosal tolerance with  $6,\infty$ 0 r in 37 fractions. In reports of experiences with electron beam therapy, Chu et al.<sup>4</sup> reported skin tolerances of  $7,\infty$ 0 rads in 35 fractions. Lochman<sup>17</sup> claimed tolerance of 7,500 rads in 5 weeks in 25 fractions. On the other hand, Zatz et al.<sup>26</sup> reported undesirable skin reactions from  $6,\infty$ 0 rads delivered in the same time period, 5 weeks, but in only 15 fractions.

All these data were both quantitatively and qualitatively in agreement with predictions from Figure 2.

Encouraged by this apparently corroborative evidence and based on the considerations summarized in Figure 2, a regimen of fractionation was developed in which at least 10, and preferably 15, fractions were employed if the field included imperiled cartilage. This system has proved to be much more satisfactory to the radiation therapist in terms of minimum cartilage complications in cases so treated.

# CONCLUSION

That the relative radiation tolerance of various anatomic tissues is a function of the number of fractions used has proved to be a useful concept. It should be borne in mind when selecting diseases for evaluation of any new modality or in comparing the experience of one reporter with that of another. Inattention to this factor may lead an observer to attribute to the modality under trial a phenomenon explicable by past experience of fractionation.

University of Washington School of Medicine Medical Radiation Physics Division Department of Radiology University Hospital Seattle, Washington 98105

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# RENAL ARTERY-PARENCHYMA RATIOS IN THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION\*

By MELVYN H. SCHREIBER, M.D.†
GALVESTON, TEXAS

HE recent medical literature contains numerous references to the value of abdominal aortography in demonstrating altered renal arterial anatomy which may be responsible for systemic hypertension. 12,84,42,56 The literature also contains many admonitions to the effect that aortography displays only the renal arterial anatomy and does not establish the relationship between renal artery stenosis, for example, and significant renal underperfusion. 23,27,28,29,35,36,43,56 The characteristic altered renal physiology in hypertension due to unilateral renal arterial underperfusion is expressed by abnormally rapid reabsorption of sodium and water on the affected side,58 and a variety of radiologic and nonradiologic tests have been devised to demonstrate these changes. Such tests include the conventional split renal function test or Howard test and its modifications, 27,29,56 the pyelogram-urea washout test, 2,3,46,49,54 the rapid sequence excretory urogram, 32,88,89 and the hydration-dehydration urogram. 6,8,26,46 The ordinary intravenous pyelogram, 5,11,52,55 the isotope renogram and the renal scan9 afford additional nonspecific information, and preoperative determination of pressure gradients across stenotic areas is feasible.2 Renal venous washout time has been determined and compared with other conventional studies in predictive value.1 An angiotensin infusion test has been devised to aid in the selection of patients who would benefit by renal revascularization or nephrectomy,80 and renal biopsy may afford valuable preoperative information. 58,80,61,82 Efforts continue to develop a simple, reliable and reproducible method for the detection and analysis of pressor substances in renal venous and peripheral blood. 25,51

When tests designed to demonstrate the characteristic altered renal physiology in renovascular hypertension have been employed in the selection of patients for surgery, cure rates have been high, 4,10,54 though some who may have benefitted from operation may have been excluded, especially those with segmental or bilateral disease. Lower cure and improvement rates have been obtained when aortography was relied upon as the chief diagnostic study prior to surgery, 18 suggesting that some of the patients operated upon had hypertension unrelated etiologically to their renal artery lesion. The present retrospective investigation was designed to study in an objective way the possibility of deriving information from aortography alone which would allow one to reliably distinguish between main renal artery lesions responsible for systemic hypertension and main renal artery lesions unrelated to the patient's hypertension or perhaps existing as a response to long continued elevation of the systemic blood pressure.

# METHOD

Abdominal aortograms were reviewed, and several measurements were made. The renal artery diameter on anteroposterior roentgenograms was measured in 3 places, at the origin of the artery from the aorta, I cm. distal to that point, and at the narrowest point of the renal artery proximal to its first division (Fig. 1A). On the same series of films, usually on the later films

<sup>\*</sup> Presented at the Thirteenth Annual Meeting of the Association of University Radiologists, Seattle, Washington, May 13-15, 1965. Department of Radiology, University of Texas Medical Branch, Galveston, Texas.
† Associate Professor of Radiology; John and Mary R. Markle Foundation Scholar in Academic Medicine.

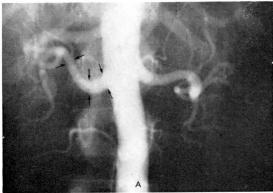




Fig. 1. (A) Renal artery diameter was measured at the origin of the artery, 1 cm. distal to that point, and at the narrowest point proximal to its first division. (B) Renal length and width were measured on later films in the series, on which a nephrogram was visible.

where a nephrogram was clearly visible, the renal length and width were measured (Fig. 1B). From these data, 11 figures were derived (Table 1): (1) renal length, (2) renal width, (3) the product of renal length and width, (4) the diameter of the artery at its origin, (5) the diameter of the artery I cm. distal to its origin, (6) the diameter of the artery at its narrowest point proximal to its first division, (7) the sum of the 3 renal artery measurements, and (8-11) the squares of the last four figures. The squared measurements afford an index of crosssectional area. From these II figures in each case, 24 ratios were derived as follows (Table II): the ratio of the diameter of the origin of the artery to renal length, width and the product of length and width; the ratio of the diameter of the renal artery I cm. distal to its origin to renal length, width and the product of length and width;

 $T_{ABLE}\ I$  eleven figures obtained and derived from the measurements taken from figure I

Mean Values—Controls									
	<ol> <li>Length</li> <li>Width</li> <li>Product</li> </ol>	13.2 6.1 81.7							
4. Origin 5. I cm. 6. Narrow 7. Sum	1.0 0.72 0.60 2.3	8. Origin <sup>2</sup> 9. 1 cm. <sup>2</sup> 10. Narrow <sup>2</sup> 11. Sum <sup>2</sup>	1.0 0.54 0.37 5.5						

the ratio of the diameter of the renal artery at the narrowest point proximal to its first division to renal length, width and the product of length and width; the ratio of the sum of the renal artery measurements to renal length, width and the product of length and width; and the ratios of the squares of these diameters and sums to renal length, width and the product of length and width. The figures thus obtained may express, in a rough pictorial way, the relationship between available blood supply and renal mass, since the diameter of the renal artery is, in general, proportional to the volume of functional renal parenchyma.33,63 Bookstein and Stewart<sup>7</sup> report no correlation between the

TABLE II
TWENTY-FOUR RENAL ARTERY-PARENCHYMA RATIOS
DERIVED FROM THE ELEVEN FIGURES IN TABLE I

Mean Values—Controls								
Origin/Length	.078	$\mathrm{O}^2/\mathrm{L}$	.078					
Origin/Width	. 168	$\mathrm{O}^2/\mathrm{W}$	.173					
Origin/Product	.013	$\mathrm{O}^2/\mathrm{P}$	.013					
ı cm./Length	.056	$_{ m I}^{2}/{ m L}$	.040					
1 cm./Width	.119	$_{ m I^{2}/W}$	.088					
ı cm./Product	.009	$_{ m I}^{2}/{ m P}$	.007					
Narrow/Length	.045	$ m N^2/L$	.028					
Narrow/Width	.097	$ m N^2/W$	.060					
Narrow/Product	.007	$ m N^2/P$	.005					
Sum/Length	.178	$\mathrm{S}^2/\mathrm{L}$	.418					
Sum/Width	.384	$\mathrm{S}^2/\mathrm{W}$	.906					
Sum/Product	.029	$\mathrm{S}^2/\mathrm{P}$	.069					

estimated reduction of the luminal crosssectional area of the renal artery and the pressure gradient across a stenotic area, except in those cases where the residual lumen was I mm. or less in diameter. That is not to infer that lesser degrees of stenosis do not produce pressure changes or decrease renal blood flow, but unless the stenotic lumen was severely reduced in diameter they could not be certain of the physiologic significance of the stenosis from the arteriogram alone. Our material was examined to determine whether or not renal artery-parenchyma ratios were reliable in predicting which patients had hypertension of renal origin, assuming that a low ratio indicated inadequate blood supply for the volume of renal tissue supplied. It is clear that many other kinds of measurements might have been chosen for such representation.

# MATERIAL

The measurements described above were made on 3 groups of subjects.

Group I consisted of 24 normal abdominal aortograms and nephrograms in 24 hypertensive patients, each of whom had had a negative pyelogram-urea washout test and each of whom was thought to have essential hypertension after thorough clinical work-up. Forty renal arteries and their associated kidneys were measured in these 24 patients. The ratios described above were determined, and ranges, means and standard deviations were determined in this control group. Patients with more than I renal artery on each side were not included.

Group II consisted of 5 patients with renovascular hypertension, proven by complete alleviation of hypertension or marked improvement following revascularization or nephrectomy. Four of these patients had positive pyelogram-urea washout tests and conventional split function studies on the affected side, and 3 of the 4 had aortographic studies showing unilateral renal artery lesions on the affected side. The fourth patient had no arterial abnormality on the side of the positive washout and Howard

tests. The fifth patient had bilateral renal artery lesions by aortography; the conventional split function study was positive on 2 occasions on the right side, and revascularization of the right side only resulted in cure of diastolic hypertension. The ratios already mentioned were determined on these 5 patients.

Group III consisted of 4 patients with lesions of the main renal artery but with negative pyelogram-urea washout tests and negative split function studies. The fourth patient in this group had a revascularization procedure on the side of the renal artery lesion without relief of hypertension. Ratios of renal artery to kidney size were determined on these 4 patients.

#### RESULTS

The ratios determined in Groups II and III were compared with the control figures determined from Group I.

In Group II, 4 of the 5 patients with renovascular hypertension showed at least 2 of the 24 ratios to be more then  $2\frac{1}{2}$  standard deviations below the mean of the control group (98 per cent confidence level). In 2 patients, 12 measurements were low and in another, 3 measurements were lower than the normal range. Table III shows renal artery-parenchyma ratios (and control values) in a patient from Group II. Asterisks mark the abnormally low figures. Figure 2 shows the aortogram of this patient, demonstrating fibromuscular hyperplasia on the right side. The remaining

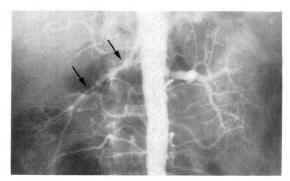


Fig. 2. Aortogram of patient shown in Table III demonstrating fibromuscular hyperplasia on the right side (arrows).

Table III

RENAL ARTERY-PARENCHYMA RATIOS (RIGHT SIDE) IN A PATIENT FROM GROUP II. CONTROL VALUES
PLUS AND MINUS 2½ STANDARD DEVIATIONS FROM THE MEAN ARE INCLUDED FOR
COMPARISON (EXAMPLE A, 125593-M)

	Control $(\pm 2\frac{1}{2}$ St. D.)					Control $(\pm 2\frac{1}{2}$ St. D.)	
Origin/Length	363	.084	(.047108)	O <sup>2</sup> /L	==	.067	. (.016140)
Origin/Width	====	. 186	(.089246)	O²/W	===	.149	(.043302)
Origin/Product	===	.020	(.005020)	$O^2/P$	====	.016	$(.\infty_{3}02_{3})$
1 cm./Length	==	.021*	(.034077)	12/L	=	.004*	(.014066)
1 cm./Width	-	.047*	(.071167)	12/W	-	.009*	(.027148)
1 cm./Product	===	.005	(.∞5013)	12/P	-	.001*	$(.\infty 2011)$
Narrow/Length	-	.OII*	(.024066)	$N^2/L$	===	. <i>001</i> *	(.0004055)
Narrow/Width	===	.023*	(.048147)	N <sup>2</sup> /W	===	.002	$(\infty 1121)$
Narrow/Product	====	.002*	(.003012)	$N^2/P$	===	.0002	(.∞∞.−.∞9)
Sum/Length	E275	. <i>116</i> *	(.127228)	S²/L	***	.126*	(.186650)
Sum/Width	===	.256	(.245524)	S²/W	-	.279*	(.353-1.458)
Sum/Product	222	.027	(.016-,042)	$S^2/P$	==	.029	(.027111)

<sup>\*=</sup> Abnormally low figures.

patient of the 5 in this group had no ratio lower than the lower limit of normal; indeed, 6 of the 24 measurements were greater than the upper limit of normal in the control group (Table IV). Thus, if an abnormally small ratio was considered to be indicative of curable renal hypertension, I of the 5 patients would have been overlooked by aortography. This patient proved to have advanced pyelonephritis and no renal artery lesion at operation, confirming

the aortographic findings shown in Figure 3. Blood pressure was significantly lowered following nephrectomy on the affected side.

There were 4 patients in Group III with obvious lesions of the main renal artery by aortography and with negative split function studies and negative pyelogram-urea washout tests. The first of these 4 patients had I renal artery-parenchyma ratio below the lower limit of normal on each side

Table IV

RENAL ARTERY-PARENCHYMA RATIOS (RIGHT SIDE) IN ANOTHER PATIENT FROM GROUP II

(EXAMPLE B, 21567-P)

			Control $(\pm 2\frac{1}{2}$ St. D.)			Control (±2½ St. D.)
Origin/Length	=	.090	(.047108)	O²/L	= .090	(.016140)
Origin/Width	===	.270!	(.089246)	O2/W	= .270	(.043302)
Origin/Product	===	.024!	(.005020)	$O^2/P$	= .024!	(.∞3−.023)
1 cm./Length	===	.054	(.034077)	r²/L	= .032	(.014066)
1 cm./Width	==	. 162	(.071167)	$1^2/W$	= .097	(.027148)
1 cm./Product	==	.015!	(.∞5013)	1 <b>2/P</b>	= .009	(.∞2ori)
Narrow/Length	==	.036	(.024066)	$ m N^2/L$	= .014	(.004055)
Narrow/Width	===	.108	(.048147)	N²/W	= .043	$(\infty_{1}121)$
Narrow/Product	==	.010	(.003012)	N2/P	= .∞4	(.∞∞1∞∞9)
Sum/Length		.180	(.127228)	$S^2/L$	= .360	(.186650)
Sum/Width	==	.540!	(.245524)	S²/W	= 1.082	(.353-1.458)
Sum/Product	==	.049!	(.016042)	S²/P	= .097	(.027111)

<sup>!-</sup> Abnormally high values. There are no abnormally low values.



Fig. 3. Aortogram of patient shown in Table IV demonstrating a small but otherwise normal right renal artery.

(Table v and vI). Aortography showed bilateral main renal artery lesions (Fig. 4), the more marked stenosis and the smaller kidney being on the left side. The second patient also had renal artery lesions on both sides; measurements on the left side disclosed II abnormally low ratios out of 24, and measurements on the right side demonstrated 10 out of 24 abnormally low figures (more than  $2\frac{1}{2}$  standard deviations below the control mean). The third patient had negative conventional split renal function and urea washout tests. Aortography showed a normal right renal artery; narrowing of the left renal artery by an

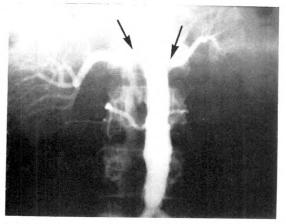


Fig. 4. Aortogram of patient shown in Table v and vi demonstrating bilateral renal artery stenosis (arrows), more marked on the left, on which side both the kidney and renal artery were strikingly small

arteriosclerotic plaque was thought to be present. No ratio was abnormally low on either side. The fourth patient, in whom revascularization on the affected side failed to effect improvement had I of the 24 ratios lower than normal (Table VII). The aortogram showed main renal artery narrowing on the right side (Fig. 5). Thus 3 of the 4 patients in Group III would have been thought to have renovascular hypertension using this criterion, and indeed I

 $T_{ABLE}\ V$  Renal artery-parenchyma ratios (right side) in a patient from group III (example a, 4056-P)

			Control $(\pm 2\frac{1}{2} \text{ St. D.})$				Control $(\pm 2\frac{1}{2} \text{ St. D.})$
Origin/Length	=	.039*	(.047108)	$\mathrm{O^2/L}$	=	.020	(.016140)
Origin/Width	=	.089	(.089246)	$O^2/W$	=	.045	(.043302)
Origin/Product	-	.007	(.005020)	${ m O^2/P}$	=	.004	(.003023)
I cm./Length	=	.055	(.034077)	$1^2/L$	=	.039	(.014066)
1 cm./Width	=	.125	(.071167)	$1^2/\mathrm{W}$	=	.088	(.027148)
I cm./Product	=	.009	(.005013)	$1^2/P$	=	.007	(.002011)
Narrow/Length	=	.039	(.024066)	$N^2/L$	=	.020	(.0004055)
Narrow/Width	=	.089	(.048147)	$N^2/W$	=	.045	(001121)
Narrow/Product	=	.007	(.003012)	$N^2/P$	=	.004	(.0001009)
Sum/Length	=	.134	(.127228)	$S^2/L$	=	.230	(.186650)
Sum/Width	=	.303	(.245524)	$S^2/W$	=	.518	(.353-1.458)
Sum/Product	=	.024	(.016042)	$S^2/P$	=	.041	(.027111)

<sup>\*</sup> Abnormally low ratio.

Table VI

RENAL ARTERY-PARENCHYMA RATIOS (LEFT SIDE) IN THE SAME PATIENT SHOWN IN TABLE V AND FIGURE 4

(EXAMPLE A, 4056-P)

			Control (±2½ St. D.)				Control $(\pm 2\frac{1}{2}$ St. D.)
Origin/Length	=	.050	(.047108)	O²/L	=	.020	(.016140)
Origin/Width	=	.125	(.089–.246)	O²/W	=	.050	(.043302)
Origin/Product	=	.016	(.∞5020)	$O^2/P$	==	.∞6	(.∞3−.023)
1 cm./Length	=	.062	(.034077)	$1^2/L$	=	.031	(.014066)
1 cm./Width	=	.156	(.071167)	$1^2/W$	==	.078	(.027148)
1 cm./Product	=	.020!	(.005013)	$1^2/P$	=	.010	$(.\infty 2011)$
Narrow/Length	=	.038	(.024066)	$N^2/L$	=	.OII	(.0004055)
Narrow/Width	=	.094	(.048147)	$N^2/W$	=	.028	$(\infty 1121)$
Narrow/Product	=	.012	(.003012)	$N^2/P$	==	.004	(.000.1009)
Sum/Length	=	.150	(.127228)	$S^2/L$	=	.175*	(.186–.650)
Sum/Width	=	-375	(.245524)	S²/W	=	.438	(.353-1.458)
Sum/Product	=	.047!	(.016042)	$S^2/P$	=	.055	(.027111)

<sup>\*</sup> Abnormally low ratio.

was operated upon without subsequent lowering of the systemic blood pressure.

# DISCUSSION

These data suggest, as has been suggested often before, that aortography alone is not adequate for the selection of patients likely to benefit from surgery for renovascular hypertension. <sup>36,48</sup> Using the ratios and criteria described here, I of 5 patients with surgically curable hypertension would have

been overlooked, and 3 of 4 patients without any other evidence of renovascular hypertension might have been selected for surgical therapy which offered little prospect of cure or improvement. It is true that 4 of the 5 patients with renovascular hypertension were correctly identified by this method; all 4 had main renal artery lesions. It appears that when reduction in renal size follows deprivation of blood supply due to main renal artery narrowing, the ratios

Table VII

RENAL ARTERY-PARENCHYMA RATIOS (RIGHT SIDE) IN A PATIENT FROM GROUP III

(EXAMPLE B, 2957-P)

			Control $(\pm 2\frac{1}{2}$ St. D.)				Control $(\pm 2\frac{1}{2}$ St. D.)
Origin/Length	=	.042*	(.047108)	O²/L	=	.017	(.016140)
Origin/Width	_	.114	(.089246)	O <sup>2</sup> /W	=	.046	(.043302)
Origin/Product	=	.012	(.005020)	$O^2/P$	==	.∞5	(.003023)
I cm./Length	=	.063	(.034077)	12/L	-	.038	(.014066)
1 cm./Width	=	.171	(.071167)	12/W	=	. 103	(.027148)
1 cm./Product	-	.018	(.005013)	1 <b>2/P</b>	=	.011	$(.\infty_{2}011)$
Narrow/Length	=	.042	(.024066)	$N^2/L$	=	.017	(.004055)
Narrow/Width	_	.114	(.048147)	N²/W	===	.046	$(\infty I 12I)$
Narrow/Product	_	.012	(.003012)	N²/P	=	.005	(.0001009)
Sum/Length	_	.148	(.127228)	S²/L	=	.213	(.186650)
Sum/Width	_	.400	(.245524)	S <sup>2</sup> /W	=	.571	(.353-1.458)
Sum/Product	_	.042	(.016042)	S²/P	=	.061	(.027111)

<sup>\*</sup> Abnormally low ratio.

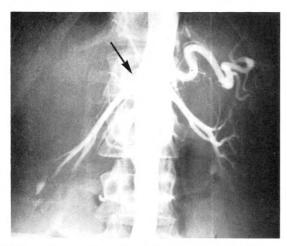


Fig. 5. Aortogram of patient shown in Table vii demonstrating main renal artery narrowing on the right side (arrow).

may be abnormally low and suggest curable renal hypertension, but there will be false positives in this group. When renal size is reduced as a consequence of some other lesion, pyelonephritis for example, followed by reduction in renal artery size with a reduction in required blood supply, the ratios may be normal or abnormally high, even in the presence of curable hypertension of renal origin. It may be that further refinements or the use of more extensive or more sophisticated measurements will increase the accuracy with which patients with other than main renal artery lesions may be identified by a ortographic measurements. For example, if more than one abnormally low ratio were required to define potentially curable hypertension from the aortogram, no additional cases of renovascular hypertension would have been missed and only I of the 4 patients with renal artery lesions but no other evidence of renal hypertension (Group III) would have been incorrectly selected for surgical therapy. Perhaps the more careful determination of renal volume from frontal and lateral studies would improve predictive accuracy with this test, but there are difficulties of superimposition to be overcome in that regard. The calculation of ratios between renal artery diameters and renal weight or volume determined from measurements of

length and width<sup>41</sup> does not produce criteria which, when used, result in different conclusions than those stated above. The ratios may have value when normal in the presence of a positive aortogram showing a lesion of the main renal artery, possibly indicating, under such circumstances, that the lesion in question is not responsible for hypertension. Additional data on this question will be sought.

It may be parenthetically mentioned that many of our aortographic studies were not suitable for determination of these ratios as they were performed by the translumbar technique without serial roentgenography, and it was only rarely that all three renal artery measurements and both parenchymal diameters could be obtained from a single film. With serial roentgenography, especially after injection into the aorta through a properly placed catheter, artery measurements could be easily made on early films, and renal length and width could be easily determined on later films during the nephrographic phase.

# CONCLUSIONS

Careful objective measurements of ratios between renal artery diameter at several points and renal length, width and the product of length and width were useful in the diagnosis of renovascular hypertension in 4 of 5 persons cured or greatly improved by operation, but use of these ratios led to incorrect diagnosis in 3 out of 4 patients with renal artery lesions and with negative conventional split function and pyelogramurea washout tests who had no other evidence of renovascular hypertension (Table VIII). While greater sophistication and perhaps more numerous measurements and comparisons might lead to increased predictive accuracy, it is felt that one or several of the available tests designed to show the characteristic altered renal physiology should be employed in addition to aortography in the selection of patients for surgery. In a recent report<sup>61</sup> of 7 patients with hypertension and renal artery lesions, 2 of whom had positive split function

TABLE VIII

SUMMARY FIGURES ON 33 HYPERTENSIVE PATIENTS STUDIED (DATA ON INDIVIDUAL PATIENTS IN GROUPS II AND III ARE SUMMARIZED)

Group	Number	Split Function	Washout Test	Aortogram
III I	24 5 4	Not done Positive Negative	Negative Positive in 4 of 4 Negative	Negative Positive in 4 of 5 Positive

# Group II (renovascular hypertension)

Patient	Normal Ratios	Low Ratios	High Ratios	
I	12	12	0	
2	9	15	0	
3	22	2	0	
4	13	3	8	
5	18	0	6	

# Group III

Patient	N	ormal Ratios	Low Ratios	High Ratios
_	R	23	I	0
1	L	21	1	2
	R	14	10	0
2	L	13	II	0
	R	24	0	0
3	L	24	0	0
4		21	I	2

studies, all of whom had bilateral biopsy evidence of arteriolar nephrosclerosis and none of whom was improved following revascularization, the need for employment of a battery of tests in the selection of patients for surgical treatment is emphasized.

Department of Radiology University of Texas Medical Branch Galveston, Texas

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# THROMBOTIC OCCLUSION OF THE ABDOMINAL AORTA\*

# ASSOCIATED VISCERAL ARTERY LESIONS AND COLLATERAL CIRCULATION

By KLAUS M. BRON, M.D. PITTSBURGH, PENNSYLVANIA

OCCLUSION of the abdominal aorta may be caused by an embolic lesion, but more commonly by thrombotic disease at the aortoiliac area, progressing retrograde. The clinical picture associated with the latter pathologic process is usually referred to as the Leriche syndrome. Since obliteration of the aortic lumen is usually gradual in this process, collateral circulation to the lower extremities has time to develop. The type and extent of the collateral channels are a valuable index in gauging the severity of the process and the ensuing clinical course.

Little appreciated is the frequency with which obliterative aortic thrombosis is associated with stenosis and/or occlusion of the major visceral arteries. <sup>18</sup> Obstruction of these vessels may occur in continuity, though not necessarily, with the obliterative aortic process as it proceeds in a retrograde direction from the bifurcation.

In the past, the diagnosis of obliterative aortic thrombosis has been suspected from the pattern of clinical symptoms and physical findings and then confirmed by translumbar aortography.1,9,16 Though this technique is adequate to demonstrate the aortic occlusion, it frequently fails to characterize the collateral circulation and associated visceral artery lesions.8 For the surgeon contemplating correction of the occlusion with a graft, the extent of the lesion and particularly the distal runoff visualized via the collateral channels are extremely important.8,4 Prior knowledge of the associated visceral artery stenoses permits repair of these lesions simultaneously at the time of grafting. This information, vital to the surgeon, can be readily obtained by the percutaneous catheter technique of arteriography.<sup>15</sup>

The present report concerns the clinical and arteriographic findings in 10 patients with abdominal aortic occlusion, and their associated visceral artery lesions and collateral circulation.

# MATERIAL AND METHOD

During the 1 year period, March, 1964 to 1965, 117 patients had arteriography in our clinic for symptoms of peripheral vascular disease. Included among these was a group of 10 with occlusion of the abdominal aorta. This group comprised 7 males and 3 females ranging in age from 44 to 68 years. The peak incidence occurred during the fifth and sixth decades. One of the 3 females was premenopausal. In 8 patients the level of the aortic occlusion was at or below the origin of the renal arteries. In 2 patients, the aortic occlusion occurred at the inferior mesenteric artery level sparing that vessel.

The technique of examination in this group of 10 patients consisted of percutaneous left transaxillary catheterization. The details of this technique in the older age group patient are described in a separate communication. A PE 240 catheter with side holes and a tip occluder was introduced into the abdominal aorta just above the site of occlusion. Serial film aortography was performed in every patient, at various aortic levels and in different degrees of obliquity, depending upon

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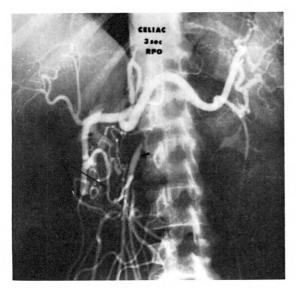


Fig. 1. Selective celiac arteriogram, right posterior oblique (RPO) view, arterial phase. The occluded superior mesenteric artery (short arrow) fills via dilated, tortuous pancreaticoduodenal arcade collateral vessels (long arrows).

the requirements of the particular case. In a small number of patients, selective arteriography of the celiac, superior or inferior mesenteric vessel was performed in order to better demonstrate the pathologic stenosis and extent of the collateral circution (Fig. 1 and 11). No complications or morbidity were encountered as the result of the transaxillary technique. There was surgical confirmation of the arteriographic findings in 8 of the 10 patients.

# CLINICAL FEATURES

The symptoms and physical findings in this group are summarized in Table 1.

#### SYMPTOMS

A remarkable feature of this group of patients with aortic occlusion is the relative absence and lack of severity of lower extremity symptoms. Hip and thigh symptoms of numbness, weakness and burning were the only ones noted in 5 patients. Calf claudication on exertion was present in 4 patients, and 2 of these also had thigh complaints. None of the patients with calf claudication felt themselves severely incapacitated by this symptom, and all received prompt relief from resting.

A finding worth commenting on is that leg symptoms in the thighs and calves may be induced by the Valsalva maneuver or straining at bowel movements. This occurred in 3 patients. A possible explanation to account for this phenomenon is the type and extent of the collateral circulation that develops to the lower extremities. The hemorrhoidal plexus is an important link in this anastomotic circulation. Straining

Table I

SUMMARY OF CLINICAL FINDINGS IN 10 PATIENTS WITH ABDOMINAL AORTIC OCCLUSION

Patient	Hip and Thigh Symptoms	Calf Claudication	Impotence	Leg Symptoms Induced by Straining	Femoral Pulses Absent Bilaterally	Temperature Change
T.W. (f)	_	_	_	_	+	+
A.W.	_	_	-	_	+	_
H.S.	+	_	_	_	+	_
F.L.	+	_	_	+	+	_
B.H. (f)	+	_	-	+	+	_
E.G.	_	+	+	_	+	_
M.K. (f)	+	+	_	_	+	+
S.S.	+	+	+	+	+	_
H.K.	_	+	_	_	+	_
N.H.	_	_	_	_	+	+
Total						
(10 Patients)	5	4	2	3	10	3

may collapse these vessels and decrease the blood flow to the lower extremities. The physiologic consequence of straining or the Valsalva maneuver is to decrease the cardiac output temporarily, and this only further adds to diminish the blood flow.

Though Leriche pointed out sexual impotence as a frequent clinical finding in this disease, the experience of others<sup>1,16</sup> and our own in this small series differs.

#### PHYSICAL FINDINGS

The salient feature that distinguishes these patients, despite their lack of significant symptoms, is the absence of femoral and more distal arterial pulses. In all 10 patients these pulses were absent bilaterally to palpation; the other physical findings were of limited value. It is interesting to note that none of these patients had leg or foot ulcers nor did their extremities appear pregangrenous.

# VISCERAL ARTERY LESIONS

The renal, celiac, superior and inferior mesenteric arteries constitute the visceral branches involved by stenosis or occlusion in association with aortic thrombotic occlusion. These findings are presented in Table II.

The renal arteries were the vessels most frequently involved by stenosis or occlusion. Three patients had only unilateral stenosis, but in 5 the process was bilateral. Occlusion occurred in only 2 patients, and in I of these there was stenosis of the other vessel. Both the right and left vessels were involved by stenosis with nearly equal frequency. Thus, in 8 of 10 patients (80 per cent), at least one or both renal arteries were stenosed or occluded. Stenosis occurred more frequently than occlusion. Diastolic hypertension was present in the 5 patients with bilateral renal artery lesions, but not in the 3 with only unilateral stenosis or occlusion. Even though hypertension was present in these patients, and renal artery lesions were found, it would be presumptuous in this age group to assume that a simple cause and effect relationship prevailed.

The celiac and superior mesenteric arteries were less frequently involved by stenosis or occlusion than the renal arteries. For each of these vessels, there was only I patient with stenosis and another with occlusion. Thus, 4 of the IO patients had either a celiac or superior mesenteric artery lesion. None of these patients had any overt gastrointestinal symptoms.

Table II

ASSOCIATED VISCERAL ARTERY STENOSES AND OCCLUSIONS IN 10 PATIENTS WITH

ABDOMINAL AORTIC OCCLUSION

Vessel	Stenosis (no.)	Per Cent	Occlusion (no.)	Per Cent	Bilateral Stenosis and/or Occlusion (no.)	Per Cent	Total Stenosis and/or Occlusion (no.)	Per Cent
Right Artery Right Left	6 5	60 50		20	5	50	8	80
Celiac Artery	I		I				2	20
Superior Mesenteric Artery	I		I				2	20
Inferior Mesenteric Artery			8	80			8	80

Table III

MULTIPLE MAJOR VESSEL STENOSES AND/OR OCCLUSIONS IN 10 PATIENTS WITH AORTIC OCCLUSION (Excluding Inferior Mesenteric Artery)

Patient	Renal		C 1:	Superior	Total	
	Unilateral	Bilateral	Celiac	Mesenteric - Artery	No.	Per Cen
1. S.S. 2. H.K.	_	_	_	=	2	20
3. T.W. 4. N.H. 5. F.L.	-	-	_		3	30
6. H.S. 7. W.A.		+++	_	_	2	20
8. M.K. 9. E.G.		+++	+	+	2	20
10. B.H.		+	+	+	I	10

The inferior mesenteric artery, because of its anatomic location, was occluded in continuity in the 8 patients with aortic occlusion at or near the renal artery level.

It is interesting to note the frequency with which multiple visceral artery stenosis and/or occlusion is associated with aortic occlusion (Table III). In 2 patients with bilateral renal artery stenosis, concurrent celiac stenosis was present in I, while superior mesenteric artery stenosis occurred in the other. A single patient had stenosis of both renal arteries plus involvement of the celiac and superior mesenteric vessels (Fig. 2). Thus, in 5 of 10 patients, either bilateral renal artery involvement alone, or in association with celiac or superior mesenteric artery stenosis was present. Only 2 of 10 patients had no associated visceral artery lesion of any type. This rather high incidence of involvement makes it imperative to adequately demonstrate these associated visceral artery lesions.

# COLLATERAL CIRCULATION

Two general anatomic systems of collateral vessels develop in response to the gradual occlusion of the abdominal aorta. <sup>12</sup> These may be designated as the viscero-

systemic and systemic-systemic pathways because of the points of origin and termination of the collateral vessels. Schematic illustrations of the more common anastomotic channels are presented in Figures 3 and 4. The arteriographic anatomy of these collateral pathways has been described from translumbar<sup>13</sup> studies and more recently from studies made by the retrograde femoral technique.<sup>6</sup>

Viscero-Systemic Collateral. This anas-

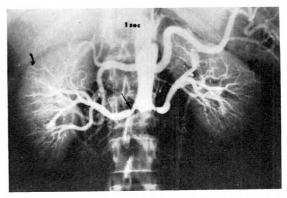


Fig. 2. A 44 year old, premenopausal woman with aortic occlusion and bilateral renal artery stenosis (straight arrows). Note the contrast filled celiac axis and lack of superior mesenteric artery visualization in this aortogram because of occlusion. Same patient as in Figure 1.

tomotic pathway comprises a single vessel, continuous from the superior mesenteric artery to the internal iliac arteries. The components of this route are the middle colic artery (a branch of the superior mesenteric artery) that in the splenic flexure region joins the left colic branch of the inferior mesenteric artery. This continues into the pelvis as the superior hemorrhoidal artery and there communicates with the middle hemorrhoidal branches of the internal iliac artery.

Systemic-Systemic Collaterals. This network is composed of a rich plexus of vessels in the flanks, back and abdominal wall, consisting of the intercostal, lumbar, internal mammary, deep circumflex iliac and inferior epigastric arteries, all providing blood to the internal and external iliac arteries. The internal iliac vessels are the hub of this system.

These two systems of collateral circulation may be equally well developed in any given patient and can then be considered balanced, or one may be dominant. The factors determining whether the systems are balanced or one dominant are the level of aortic occlusion, the severity of the obstructive process, stenosis of the superior mesenteric artery and patency of the internal iliac vessels.

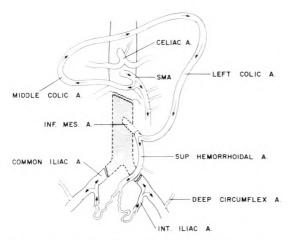


Fig. 3. Composite schematic drawing of the viscerosystemic collateral circulation in 8 patients with aortic occlusion at the renal level. The shaded area represents the occluded portion of the aorta.

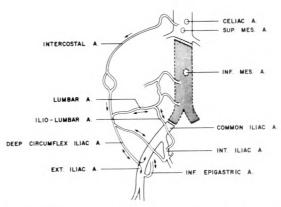


Fig. 4. Composite schematic drawing of the systemic-systemic collateral pathways in abdominal aortic occlusion. The shaded area represents the occluded portion of the aorta.

When aortic occlusion occurs at the inferior mesenteric artery level as shown in Figure 5, the main collateral channels are via the lumbar and lower intercostal arteries. This typifies systemic-systemic collateral dominance and the viscero-systemic pathway, though potentially available, is not well developed.

As the level of aortic occlusion progresses retrograde to the renal arteries, the type of dominant collateral circulation varies. In 3 patients the viscero-systemic channel was dominant, shown by total aortography (Fig. 6) and better illustrated by selective arteriography (Fig. 7). This usually indicates that the obliterative process has involved the origins of the intercostal arteries above the level of the occlusion. Balanced, or equally well developed viscero- and systemic collaterals were noted in 3 patients. Dominant systemic-systemic anastomoses were present in 2 patients, with occlusion at this level. One of these patients had stenosis of the superior mesenteric artery (Fig. 8) and the other had occlusion of the internal iliac arteries (Fig. 9).

The frequency of distal runoff or reconstitution of the pelvic vessels, demonstrated by the collateral channels, is shown in Figure 10. The common iliac vessels were least frequently demonstrated. This confirms the frequency with which these ves-

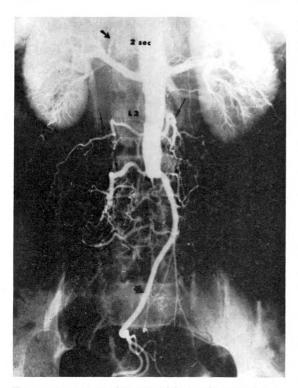


Fig. 5. A 55 year old man with aortic occlusion at the inferior mesenteric artery level. Typical systemic-systemic collateral dominance with prominent lumbar arteries (thin arrows) and intercostal arteries (slant-tailed arrow). Dilated superior hemorrhoidal artery (broad arrow head).

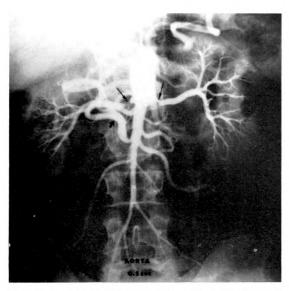


Fig. 6. A 50 year old man with aortic occlusion and bilateral renal artery stenosis (thin arrows). Viscero-systemic collateral dominance established by a dilated and moderately tortuous middle colic

sels are affected by the same occlusive process as in the aorta. The external and internal iliac vessels are most frequently visualized by arteriography. When the viscero-systemic collateral channel is the main anastomotic route, it may be necessary to selectively catheterize the superior mesenteric artery to visualize the runoff (Fig. 11). This enables the maximum amount of contrast material to reach the pelvis and outline the internal iliac arteries.

# DISCUSSION

Thrombotic occlusion of the abdominal aorta is the end stage of a gradually progressive process that usually begins at or near the aortic bifurcation. In association

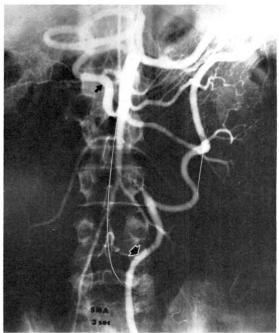


Fig. 7. Selective superior mesenteric arteriogram (SMA) of the same patient as in Figure 4. This demonstrates the visceral collateral pathways, comprised by the middle colic artery (thick arrow), the left colic artery and the superior hemorrhoidal artery (arrow head). Note the size of these vessels.

artery (thick arrow), a branch of the dilated superior mesenteric artery. Note the lack of intercostal or systemic arteries. with this aortic process, the major visceral branches may be stenosed or occluded. These lesions are probably caused independently but by the same etiologic factors responsible for the aortic lesion, and there appears to be a certain predilection for the renal arteries. Occasionally, the visceral branches are involved as the result of direct extension of the aortic thrombosis into the branch vessels. Whichever of these mechanism is ultimately responsible for the visceral branch lesions is of less significance than recognition and confirmation that the lesions are present.

The collateral circulation that develops to maintain blood flow to the lower extremities follows a variety of pathways. The level of the aortic occlusion determines to a large extent the type of collateral circulation. The potential anastomotic routes nearest to the site of occlusion are the ones that respond most vigorously. Thus, occlusion near the aortic bifurcation causes the lumbar arteries to dilate and maintain

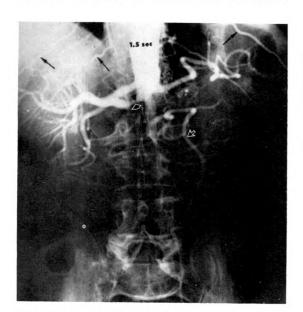


Fig. 8. A 68 year old man with aortic occlusion and superior mesenteric artery stenosis. Right renal artery stenosis (solid arrow head) and left renal artery occlusion with intercostal collateral vessels to the patent distal left renal artery. Systemic-systemic collateral dominance illustrated by the prominent intercostal arteries (thin arrows) and meager visceral collaterals.



Fig. 9. A 52 year old man with aortic occlusion at the renal artery level. The systemic-systemic collaterals are dominant, demonstrated by the deep circumflex iliac artery (thin arrow) filling the common femoral (arrow head). Note the small superior hemorrhoidal artery (thick arrow) and nonfilling of the internal and external iliac vessels, bilaterally.

lower limb circulation, whereas occlusion in the more proximal portion results in both viscero-systemic and systemic-systemic pathways.

Angiography is the only diagnostic procedure, short of surgery, that can confirm

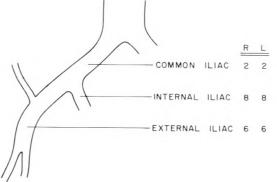


Fig. 10. A summary of the frequency with which the pelvic vessels were demonstrated via collateral circulation, reflecting their patency, in 10 patients with abdominal aortic-occlusion.

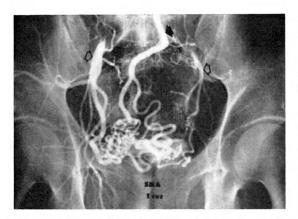


Fig. 11. Demonstration of the pelvic runoff via selective superior mesenteric arteriography. The superior hemorrhoidal artery (solid arrow head) anastomoses through dilated and coiled middle hemorrhoidal branches with the internal iliac arteries (open arrowheads). Same patient as in Figure 5 and 6.

the clinical evaluation of this entity. The technique employed is important since the extent of the occlusion must be adequately defined. This implies that the distal runoff must be demonstrated as well as any associated branch stenoses. Translumbar aortography has been faulted for not meeting these requirements.<sup>5,8</sup> The percutaneous transaxillary catheter approach readily yields all the desired information when investigating this lesion. Further, it offers some very definite advantages over the translumbar technique in patients with this disease. The site of obstruction is approached from above and eliminates the danger of possibly puncturing the aorta directly through an area of thrombosis. The visceral vessels may be selectively catheterized to better demonstrate collateral circulation to the pelvis and between visceral branches. The patient may be easily turned into various degrees of obliquity, to best demonstrate certain features, depending on the nature of the findings. And lastly, the potential hazards of general anesthesia are avoided since percutaneous catheterization is usually performed with only moderate analgesia.

The disparity between the bizarre arteriographic findings and relative lack of

clinical symptomatology in aortic occlusion can only be explained by the adequate collateral circulation. Thus, the usual symptoms of peripheral vascular disease, intermittent claudication, temperature variations and paresthesias are not pronounced. These symptoms become more evident as the thrombotic process progresses and involves more of the potential anastomotic pathways.

The interesting feature that straining produced symptoms in a number of these patients may prove to be clinically useful in differentiating between proximal and distal abdominal aortic occlusion. In proximal occlusion the visceral collateral channel via the hemorrhoidal arteries is an important route that may be compromised during straining. However, in distal aortic occlusion, the visceral collateral is usually an insignificant pathway and, thus, its compromise should not affect blood flow to the lower extremities.

# SUMMARY

A group of 10 patients with abdominal aortic occlusion was studied by percutaneous transaxillary arteriography. This technique proved to be a simple and safe method of demonstrating the level of occlusion, the associated visceral artery lesions, the collateral circulation and the distal runoff. The clinical symptoms and physical findings commonly encountered in this disease are briefly described. Associated visceral artery stenosis and/or occlusion occurred in 80 per cent of patients with aortic occlusion, and the renal arteries were the vessels most frequently affected. Two general systems of collateral channels, the visceral and systemic pathways, develop in response to aortic occlusion. The arteriographic anatomy of some of these various pathways is presented and factors that determine why one may be dominant are discussed.

Presbyterian-University Hospital 230 Lothrop Street Pittsburgh 13, Pennsylvania The author wishes to express his thanks to Drs. L. Reed Altemus and Louise Sherman for their valuable assistance in performing these studies, and to Mr. Joseph Glessner for his excellent technical help.

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# DETERMINATION OF THE BLOOD FLOW BY A RADIOGRAPHIC TECHNIQUE\*

# PHYSICAL CONSIDERATIONS AND EXPERIMENTAL RESULTS

By SADEK K. HILAL, M.D., Ph.D. (Radiol.)†
NEW YORK, NEW YORK

METHOD for the quantitative densi-1 tometric study of clinically obtained roentgenograms has been developed and used for the determination of blood flow rates in individual arteries. The application of this method to regional cerebral flow determination is currently under investigation. In this report the mathematical background and the physical factors concerned with the quantitative recovery of data from the roentgenograms will be discussed, and the results obtained from animal experiments will be presented. The hemodynamic changes associated with contrast medium injection and results of the human carotid flow determination will be presented separately.5,6

The determination of the blood flow rate in a vessel by a radiographic technique is an indicator dilution method using a radiopaque indicator. The contrast medium is injected at a known constant rate in the artery of interest and the final dilution of the opaque solution by the blood stream is determined from densitometric measurements on the roentgenogram. The rate of blood flow is calculated according to the Hamilton-Stewart formula:<sup>22</sup>

Flow (liters/min.)

Figure 1, A and B illustrates the principle of the radiographic indicator dilution

method. The artery with high flow rate shows a low contrast on the roentgenogram as a result of the greater dilution of the opaque medium.

### METHODS

# A. MATHEMATICAL BASIS

The absorption of x-rays in matter is expressed by the following equation: 7.8

$$I = I_{\bullet} \cdot e^{-(\mu.\text{cm.})}, \qquad (2)$$

where

I<sub>0</sub>= the intensity of the incident beam,
 I = the intensity of the x-ray beam after attenuation by the absorber,
 μ= the linear absorption coefficient,
 cm. = the thickness of the absorber.

The following equation can be derived:

$$I = I_o \cdot e^{-[(\mu/\rho) \cdot \rho \cdot \text{cm.}]}, \tag{3}$$

where  $\rho$  is the density of the x-ray absorber expressed in gm./cm.<sup>3</sup> or its concentration in gm./cm.<sup>3</sup> of solution when the absorber is a soluble substance.

If  $\mu/\rho$  is the mass absorption coefficient m, equation (3) can be rewritten:

$$I = I_o \cdot e^{-\mathbf{m} \cdot C \cdot d}, \tag{4}$$

where C is the concentration of the absorber in gm./cm.<sup>8</sup> and d the diameter in cm. of the tube or the artery containing the absorber.

The ratio between the intensity of the incident x-ray beam and the intensity of the transmitted beam through the iodine containing artery represents the degree of

<sup>\*</sup> The work presented in this paper has been awarded the Annual Memorial Medal of the Association of University Radiologists in May, 1962.

From the Department of Radiology of the University of Minnesota, Minnesota, Minnesota. Supported by Grant #HE 06927 of the National Institute of Health.

<sup>†</sup> Assistant Professor in Radiology at the Neurological Institute, Columbia Presbyterian Medical Center, New York, New York.

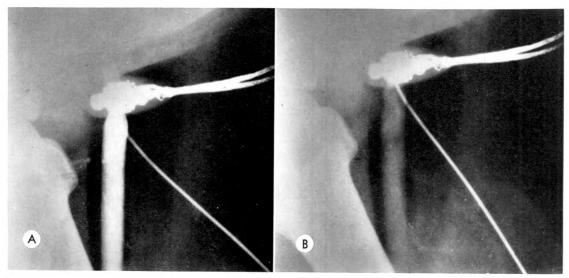


Fig. 1. Argiograms of 2 femoral arteries in the dog with different blood flow rates: 70 ml./min. in (A) and 400 ml./min. in (B). The rate of injection of the contrast medium was identical in the two cases. In the artery shown in (B) the radiopaque medium is markedly diluted by the high blood flow rate resulting in a diminished optical contrast of the vessel. The electromagnetic flowmeter is seen near the top of the picture and the injection catheter is on the right.

the attenuation of the x-ray by the artery. This ratio will be called *attenuation factor* (A. F.):

$$(A.F.) = I/I_o = e^{-m.C.d},$$
 (5)

and

$$\log_e(A.F.) = \log_e I/I_o = -m.C.d.$$
 (6)

In equation (6) if m and d are maintained constant,  $log_{e}$  (A.F.) will vary linearly with the concentration C. The curve representing this linear relation will be called the attenuation curve. Experimentally, m and d are maintained constant by the use of a set of tubes of identical diameter containing various concentrations of the same iodinated indicator. This set of tubes will be incorporated into a plexiglass block called the *iodine standard* which will be described in detail later.

The attenuation factor of each of the tubes of the iodine standard is determined by the measurement of the optical density of their radiographic image (Fig. 2). The density of the film in the area immediately adjacent to the image of the tube is a function of the intensity of the incident x-ray beam unattenuated by the iodine in the

tube, while the lighter optical density of the image of the tube is a function of the attenuated transmitted beam. If the photographic response of the film screen combination to the radiographic exposure is known, then the attenuation factor of the iodine containing tube can be determined from the measurement of the optical density of the image of the tube and its background on the roentgenogram.

The photographic response of the film screen assembly has been determined experimentally and a curve has been fitted to the obtained results (Fig. 3). The obtained function is:1,11,21

$$D = D_{\infty}(\mathbf{I} - e^{-\gamma E}) - n$$

$$-\log_{e}\left(\mathbf{I} - \frac{D+n}{D_{\infty}}\right), \tag{7}$$

where:

E=relative exposure expressed in empirical numbers,

D=optical density obtained by the densitometric measurement,

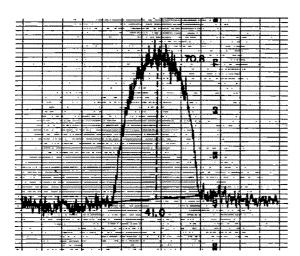


Fig. 2. The densitometric tracing of one of the tubes of the *iodine standard*. The *attenuation factor* is calculated from the light transmittance at the top of the curve (70.8 per cent), and from the light transmittance in the middle of the base line (41 per cent). The corresponding optical density is the logarithm of these values. The two relative roentgen exposures necessary to produce these two densities are calculated from the sensitometric curve. The ratio of these two exposures is the attenuation factor.

D∞ = optical density of the film at saturation exposure. This is a constant value which depends on the amount of the silver content of the photographic emulsion and the size of the silver grain,

n and  $\gamma$  = constants which depend on a variety of factors like the developing process and the sensitivity of the film.

If the optical density of the image of the tube is D and the corresponding relative exposure is E, and the optical density next to the image of the tube is  $D_0$  and its corresponding relative exposure is  $E_0$ , the attenuation factor of the tube is then:

$$(AF.) = \frac{I}{I_o} = \frac{E}{E_o} = \frac{\log_e \left( I - \frac{D+n}{D_\infty} \right)}{\log_e \left( I - \frac{D_o+n}{D_\infty} \right)} \cdot (8)$$

From this equation, it is obvious that the attenuation factor is independent of the constant value  $\gamma$  and its dependence on the remaining two constants n and  $D_{\infty}$  is only minimal since they appear in both sides of the fraction. It was found experimentally that a 25 per cent error in the determination of either  $D_{\infty}$  or n will usually result in a variation of 1 per cent only in the value of the attenuation factor. It is this stability that made the accuracy of this work possible.

The attenuation factors of various tubes of the iodine standard are determined from the densitometric readings and an attenuation curve is drawn (Fig. 4, A and B). The attenuation factor of the artery studied is likewise obtained from the densitometric data. Using the attenuation curve of the iodine standard, the concentration of the contrast agent which will attenuate the x-ray to the same extent as the artery is determined as shown in Figure 4B. This is called the equivalent standard concentration  $(C_i)$ . Since both the tube containing the equivalent standard concentration and the artery studied have the same attenuation factor, the following equation can be derived from equation (6):

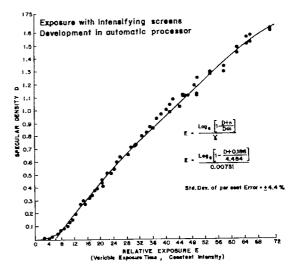


Fig. 3. Kodak Blue Brand characteristic curve: the sensitometric curve of the radiographic film obtained with a variable exposure time and a constant intensity.

$$Log_{e}(A.F.) = -mC_{t}d_{t} = -mC_{a}d_{a}$$

$$\frac{C_{t} \cdot d_{t}}{d_{a}} = C_{a},$$
(10)

where  $C_t$  is determined from the attenuation curve as mentioned above,  $d_t$  is the diameter of the tube of the iodine standard and  $d_a$  is the diameter of the artery as measured on the roentgenogram and corrected for the magnification.  $C_a$  is the actual concentration of the indicator in the artery. The flow is then calculated using equation (1) as follows:

Flow (ml./min.) = Rate of injection of the opaque (ml./min.)

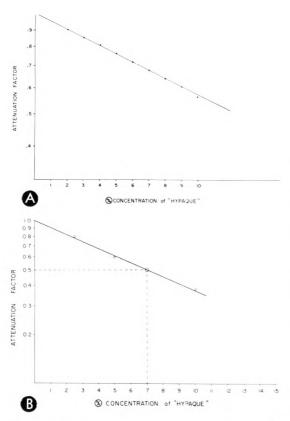


Fig. 4. (A) Attenuation curve obtained from the iodine standard. (B) The method of determining the equivalent standard concentration of the artery from the attenuation curve. In this case the vessel has absorbed 50 per cent of the x-ray beam which is equivalent to a standard tube containing 7 per cent hypaque.



Fig. 5. The densitometer.

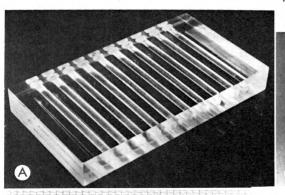
Per cent concentration of (11)  $\times \frac{\text{injected material}}{\text{Per cent concentration of the}}$ opaque in the artery ( $C_a$ )

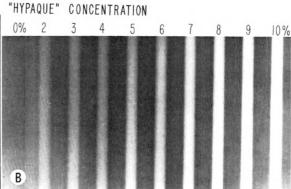
B. APPARATUS

The Densitometer (Fig. 5). A specular densitometer designed for spectrographic analysis has been used in this work.\* The scanning light beam is 40 micra in width and 0.75 mm. long. The scanned field is magnified 15 times and projected on a large frosted glass screen. This arrangement permits the accurate localization of the light beam on the roentgenogram, which is scanned along a straight line running perpendicular to the image of the artery or the tubes of the iodine standard. The changing optical density is traced on a 10 inch wide, strip chart recorder.

The Iodine Standard (Fig. 6, A, B and C). Ten blind holes measuring 6 mm. in diameter and 80 mm. in depth are drilled in a plexiglass block measuring 2.5×10×20 cm. Hypaque solutions of 9 different concentrations ranging from 2 to 10 per cent are prepared with preboiled distilled water. One hole of the plexiglass block is filled

<sup>\*</sup> Available from the National Spectrographic Laboratories Cleveland, Ohio.





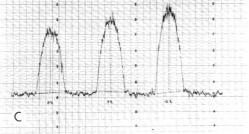


Fig. 6. (A) The iodine standard. (B) A roentgenogram of the iodine standard. (C) Densitometric tracing of the roentgenogram of the iodine standard.

with preboiled distilled water and each of the remaining 9 holes is filled with one of the hypaque solutions. The open ends of these holes are then sealed with a plexiglass plug.

The Injector (Fig. 7). A special injector has been built to permit the accurate constant rate injection of the viscous radiographic contrast media through the long thin catheters used in this study. Injection rates varying from 25 to 600 ml./min. are possible.

Catheters. In order to ensure adequate mixture of the contrast agent and the

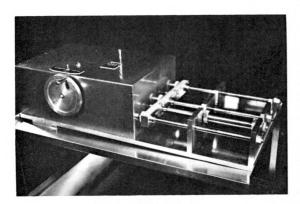


Fig. 7. The injector.

blood, the injections are made through a closed end catheter with multiple side holes. A very small teflon tubing (I.D. = 0.53 mm., O.D. = 0.816 mm.) has been used for these injections. Because of its small size, this catheter can be threaded through a carotid puncture needle or through an angiographic catheter. In the experimental work, this small catheter has been introduced through a side branch of the femoral artery in the dog.

# C. PROCEDURES

I. The Determination of the Characteristic Curve of the Radiographic Film. Sheets of Kodak Blue Brand Radiographic Film mounted in a par speed screen cassette were separately exposed to a diagnostic x-ray beam of fixed intensity while the exposure time was varied from I second to 100 seconds. The experiment was carried out in an air conditioned room to avoid significant changes in the ambient temperature. The films were developed in the Kodak automatic processor. The graph in Figure 3 represents the results obtained from 67 films and the equation of the fitted curve is given with the standard error. Correction

for fog has been made according to the method recommended by Pritchard.<sup>16</sup>

- 2. The Flow Model Experiment. Water containing a small amount of detergent was siphoned from 2 five-gallon containers (Fig. 8) through a polyvinyl tube. The detergent minimizes the formation of air bubbles in the system. The water flowed at a constant rate through a plexiglass block (12 cm. thick) placed on the radiographic table to serve as a radiographic phantom. From this phantom, the water flowed through a plastic tubing into a graduated cylinder. The rate of flow was controlled by an adjustable clamp fitted on the distal end of the plastic tubing. The quantity of water collected in the cylinder in a period of I minute is a direct measurement of the flow rate. The contrast material was injected upstream and very close to the plastic phantom through a closed end teflon catheter. In every experiment, the flow rate was determined directly and roentgenographically. A roentgenogram of the flowing mixture of contrast material and water through the phantom was taken I second after the beginning of the injection.
- 3. Determination of the Canine Femoral Flow. Mongrel dogs weighing about 15 kg. were anesthetized with surital. The femoral artery was exposed and an electromagnetic flowmeter<sup>9,10</sup> probe was placed around the femoral artery just distal to the inguinal ligament. The small teflon catheter was introduced into the common femoral artery through one of its muscular branches. In its final position, the tip of the catheter lies about 2 cm. distal to the probe. All the branches of the femoral artery between the catheter tip and the probe were ligated. A cannula was introduced in the femoral artery of the opposite side for continuous pressure recording. Zero calibration of the flowmeter by arterial occlusion and accurate measurement of the femoral flow and the systemic pressure were performed before each injection of radiopaque material. Hypaque 50 per cent was used in these experiments. One second after the beginning of the injection, the roentgenogra-

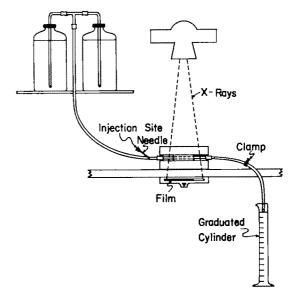


Fig. 8. The flow model.

phic exposure was made for I or 2 seconds, at the end of which the injection was stopped. This long exposure was intended to average systolic and diastolic flow.

After the end of the injection, another roentgenogram of the same area was taken with the iodine standard superimposed. A metallic disk was positioned at the level of the artery to permit the calculation of the roentgenographic magnification. The exposure factors were kept constant for both roentgenograms. A 12:1 moving grid and a 12:1 stationary grid were used in a cross-hatched arrangement.

## RESULTS

Some of the results of the flow model experiments are presented in Table 1. The variation in the size of the arteries was simulated by changes in both the flow rate and the diameter of the tube in the flow model. These changes did not cause any observable change in the accuracy of the method.<sup>4</sup> Table 11 shows some of the results obtained from the femoral artery experiments in the dog. The deviation of each of the results from the corresponding control is presented as the percentage error in a separate column. The standard error and the correlation coefficient of each set

TABLE I
FLOW MODEL EXPERIMENTS

Experi- ment No.	Actual Flow ml./min.	Flow by Radiography ml./min.	Percentage Error
I	450	453	+ .6
2	448	453	+r.r
3	245	244	5
4	244	261	+6.9
5 6	144	145	<b>-</b> .6
6	45	46	-2.2
7	68	63.5	-3.5
8	68	71	+4.4
9	105	115	+9.5
IO	260	267	+2.7
II	443	426	-3.9
12	44 I	43 I	-2.3
13	247	247	0
14	244	243	-0.4
15	70	72	+2.8
16	68	69	+1.5
17	68	72	+5.8

Standard deviation of the percentage error = ±3.8%. Standard deviation of the differences = ±7.46 ml./min. Correlation coefficient: r=0.998 (P <0.001).

of data are also shown. The statistical analysis has been made according to the methods of Fisher.<sup>2</sup>

The close correlation of the results obtained form the electromagnetic flowmeter and from the radiographic method (r =0.996, P<.001) suggests that the accuracy of the two methods is of the same order. This demonstrates the adequacy of the radiographic technique for the application in the vast majority of the clinical situations where changes in the flow due to pathologic processes are larger than the technical errors observed here.

# DISCUSSION

Various factors were investigated to study their effect on the accuracy of the quantitative recovery of data from roentgenograms and are discussed in the following paragraphs.

# A. FACTORS AFFECTING THE RADIOGRAPHIC CONTRAST

The method presented here for the determination of the concentration of contrast medium in the arteries depends on the measurement of the radiographic contrast of the injected vessel. In view of this, all the technical factors causing any variation of this contrast will have to be adequately controlled.

The slope of the attenuation curve obtained from the iodine standard is a measure of the radiographic contrast of this test object. Factors decreasing this contrast will result in a decrease of the slope of the attenuation curve. In this work the various technical factors affecting the radiographic contrast are evaluated by the study of their effect on the attenuation curve. As it will become apparent, this method proved to be accurate and yielded significant information about various points in the same radiographic field.

1. Effect of the Energy and the Filtration of the X-ray Beam on the Radiographic Contrast. As shown in Figure 9, an increase in the kv. peak diminishes the radiographic contrast, resulting in the decrease of the

 $\label{eq:Table II} \textbf{Femoral artery flow in the dog}.$ 

			·····
Experi- ment No.	Flow by Electro- magnetic Flow- meter ml./min.	Flow by Radio- graphy ml./min.	Percentage Error
I	80	88	+ 9.1
2	120	111	- 8.1
3	108	102	- 5.5
	401	352	-12.2
4 5 6	76	87	+12.7
6	75	78	+ 4.0
7	79	8 <i>5</i>	+ 7.5
8	82	80	- 2.5
9	73	80	+9.5
10	99	107	+ 7.5
ΙΙ	114	117	+ 2.6
12	106	97	- 8.5
13	99	98	- I.O
14	120	129	+ 7.0
15	111	120	+ 8.5
16	104	102	<del>-</del> 1.9
17	118	117	- 1.0

Standard deviation of the percentage error =  $\pm 7.4\%$ . Standard deviation of the differences =  $\pm 14$  ml./min. Correlation coefficient: r=0.996 (P <0.001).

slope of the attentuation curve. Additional filtration has the same effect.

In order to reduce the unpredictable filtering effect of the soft tissues surrounding the artery on the x-ray, the incident x-ray beam must be heavily pre-filtered. It was found experimentally that 0.42 mm. of copper is adequate, as shown in Figure 10 where an additional 15 cm. of plexiglass did not change the quality of the filtered x-ray beam as demonstrated by the copper absorption curve.

Ninety kv. peak was chosen for most of the work presented here because at this energy level x-ray absorption occurs mostly by the Compton process which shows little dependence on the wave length. The high kilovoltage and the heavy filtration resulted in an x-ray beam that acted in effect as a monochromatic ray.

2. Effect of the Scattered Radiation on the Radiographic Contrast. 12,18 The scattered radiation diminishes the radiographic contrast. This factor has also been evaluated with the use of the attenuation curve as shown in Figure 11 and Figure 12. The scattered radiation is more significant in the center of the field where the contrast is most decreased. This is well demonstrated in the top curves of Figures 11 and 12, where the attenuation curves show an up-

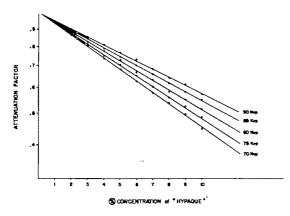


Fig. 9. Attenuation curves of the iodine standard obtained from roentgenograms exposed with various energies ranging from 70 to 90 kv. peak. The decrease of the slope of the curve with the increased energy is well demonstrated.

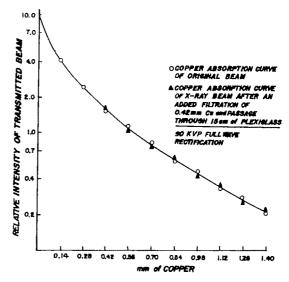


Fig. 10. The copper attenuation curve of the x-ray beam. The triangles represent the curve obtained from a beam filtered with 0.42 mm. of copper and after its passage through a 15 cm. plexiglass block. This highly filtered beam does not show any change in quality after passing through plexiglass.

ward bulge corresponding to the tubes containing 5 and 6 per cent hypaque. These tubes are in the middle of the radiographic field. This uneven distribution of the scattered radiation ceases when a crosshatched grid or a 40 inch air gap is used. It is interesting to note that, when an air

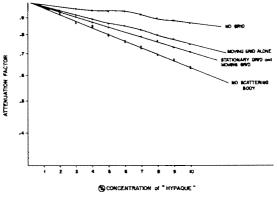


Fig. 11. Attenuation curve obtained from the roentgenogram of the iodine standard for the comparison of the efficiency of various grids. Ninety kv. peak x-rays and an added filtration of 0.42 mm. of copper were used. Twelve cm. thick plexiglass block was employed as a scattering body. Poor radiographic contrast is observed when no grid is used, as seen on the top curve. The contrast improved as more grids were added.

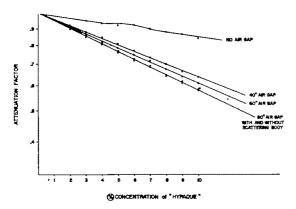


Fig. 12. Same experiment as in Figure 11 for the study of the effect of various air gaps on the radiographic contrast. The slope of the attenuation curves increases as larger air gaps are used, indicating an improvement in the radiographic contrast.

gap of 80 inches was left between the 12 cm. thick plexiglass scattering block and the film, the scattered radiation did not produce any photographic effect and the contrast of the image was not decreased by the plexiglass block. It was also found that the grid introduced additional filtration, resulting in a slight decrease of the slope of the attenuation curve.

# B. PHOTOGRAPHIC ARTIFACTS

1. Fog. In this work an unexposed radiographic film from the same package is routinely developed and its density measured. The relative exposure  $E_f$  corresponding to this density is determined using equation (7). The correction for the fog is made as follows:

$$E = E_1 - E_f$$

where  $E_1$  is the relative exposure corresponding to the total density of the film including the fog, and E is the net relative exposure due to the x-rays. It can be demonstrated mathematically that this method of correction for the fog is almost identical with the method suggested by Wisley.<sup>26</sup>

2. The Failure of the Reciprocity Law. The curve of Figure 3 was obtained using exposures of varying durations and a constant intensity beam. The radiographic film, from which the calculation of the con-

centration is made is, on the other hand, exposed to a beam of varying intensity. The effect of the failure of the reciprocity law will thus have to be considered. It can be shown mathematically using the Schwarzschild equation that the failure of the reciprocity law will cause a change in the slope of the attenuation curve of the iodine standard without distorting its linearity. This is proven by the experiment illustrated in Figure 13. In one-half of the radiographic field, the film was exposed to the x-ray beam directly while in the other half this beam was attenuated by various thicknesses of plexiglass.

In view of the fact that this linearity of the attenuation curve of the iodine standard is maintained in spite of the failure of the reciprocity law and in view of the fact that the radiographic density of the artery and the density of the standard tubes with which it is compared are affected to the same extent by this irregular response of the photographic emulsion, the calculation of the concentration of the radiopaque indicator in the artery using the method de-

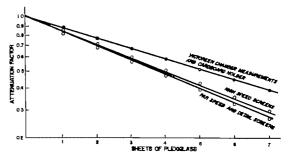


Fig. 13. The plexiglass attenuation curve of the x-ray beam calculated from measurements made using the ionization chamber and from the roentgenograms made with a cardboard holder and with cassettes containing screens of various speeds. The ionization chamber measurements and the values obtained from the cardboard holder are identical. On the other hand, the attenuation curve obtained with the intensifying screen exposures and calculated with data from a time scale sensitometric curve shows increased contrast (an increased slope). This is the result of the failure of the reciprocity law. The high speed screens show a diminished contrast, probably due to the fact that they contain some lead salts and thus absorb more of the higher energy photons.

scribed here remains accurate and unaffected by the reciprocity law failure.

3. The Effect of the Modulation Transfer Function on the Flow Determination. The limited modulation transfer ability of the screen will result in the limitation of the usefulness of this method when small vessels are studied. It has been demonstrated by a graphical technique of reconstruction of the cross-section of the artery<sup>4</sup> that this method can be used only when the image of the artery is larger than 2 to 3 mm. in diameter, depending on the type of intensifying screen used.

# C. EVALUATION OF THE RADIOGRAPHIC SAMPLING METHOD

In all of the indicator dilution techniques, there is an injection site and a sampling point where the concentration of the injected material is determined. This radiographic approach to blood flow determination differs from the standard dye dilution methods only in the sampling technique: here the concentration of the iodinated indicator is determined from the measurement of the optical density of the roent-genogram. This radiographic sampling offers a few advantages.

- I. The Closeness of the Injection and Sampling Sites. This subject has been reviewed by Visscher and Johnson, 25 Stow, 28 Rossi et al., 17 and Fox and Wood, 8 who recommend the approximation of the injection and sampling sites and the avoidance of sampling from a branch of the main stream. In the radiographic method, the sampling is within a few centimeters of the injection point.
- 2. The Reduction of the Error Due to Inadequate Mixing of the Indicator. In the radiographic method, the turbulence produced by the injection results in a uniform velocity front<sup>24</sup> at the nearby sampling site, thus reducing the error due to the slow moving layers of the blood stream in contact with the artery wall when a laminar flow is maintained. This turbulence has been studied by rapid sequence cinematography in the flow model and the evidence

supports the view expressed above.

In addition to the beneficial effect of the turbulence, the error due to inadequate mixing of the indicator is further reduced by the fact that in the radiographic method the whole cross-section of the artery is sampled by the x-ray beam. The attenuation of this beam is a function of the total amount of iodine encountered in its path, regardless of the uneven distribution of this indicator. Usually, the densitometric curve resulting from the scanning of the image of the artery has a regular contour, indicating an even distribution of the contrast medium throughout the cross-section of the vessel. In the cases where this curve is asymmetric, multiple determinations of concentrations are made at various points on this curve and an average concentration is computed.

- 3. The Reduction of the Error Due to Recirculation of the Indicator. The arteriogram of the injected artery is completed about 4 seconds after the beginning of the injection, leaving no sufficient time for the opaque material to recirculate through the sampling site. The accumulated contrast medium in the blood is partially excreted by the kidneys and the retained amount is insufficient to produce a detectable density, interfering with repeated tests.
- 4. Finally, this method makes the determination of the blood flow rate in a single peripheral artery possible as a clinical test.

# CONCLUSION AND SUMMARY

A method for the quantitative data recovery from arteriograms has been developed and used for the determination of the blood flow rate in a single peripheral artery. A study of the various physical factors affecting the accuracy of this technique is presented.

A close correlation was found between the results obtained by the radiographic technique and those obtained by the direct measurement in the flow model or by the electromagnetic flowmeter in the canine femoral artery experiments (r=0.996,  $P<.\infty I$ ).

The errors resulting from the technical aspects are smaller than the variations expected to be caused by the pathologic processes.

A comparison of this method with the conventional dye dilution techniques is presented and the advantages of the radiographic sampling are discussed.

Neurological Institute 710 West 168th Street New York, New York 1∞32

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# A TECHNIQUE FOR SLIT SCANOGRAPHY\*

By JOHN H. WOODRUFF, Jr., M.D.,† and GERALD LANE, R.T.‡
LOS ANGELES, CALIFORNIA

THE principles of radiologic measurements of the extremities are well known. The Bell-Thompson¹ method was employed in our hospital for many years with somewhat erratic results. This method requires a precise orientation of the central ray in relation to the points of reference for accuracy. This was too frequently improperly accomplished by our technical staff. Efforts to solve this by training were not entirely successful due to technician turnover and the limited demand for the procedure.

# MEASUREMENTS WITH FLUOROSCOPIC CONTROL

Our first approach to this problem was to make spot roentgenograms during image intensified fluoroscopy. The precise centering over the points of reference could thus be controlled by the fluoroscopist. A special rule had to be constructed as unfavorable geometry precluded visualization of the markings on our Bell-Thompson rule. This method also had the disadvantage of added radiation exposure from the fluoroscopy and required a radiologist for its accomplishment. The speed and precision possible were some compensations.

# ANOTHER COMMON METHOD

Use of a long cassette with precise centering over the points of reference permits a direct measurement from the roentgenogram with no requirement for a rule. The need for exact centering over the points to and from which measurements are made is the same as for the other methods discussed above.

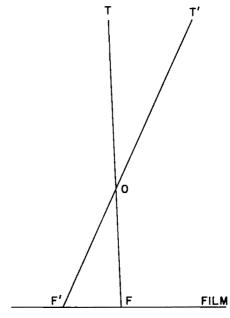


Fig. 1.

- O=A point to be measured in the object.
- T=A point on the target, the origin of an x-ray intersecting O and perpendicular to the film at F.
- T'=A point on an improperly centered target, the origin of an x-ray intersecting O and not perpendicular to the film at F'.

FF'=The measurement error.

Triangles TOT' and FOF' are similar. Therefore

$$\frac{FF'}{TT'} = \frac{OF}{OT}$$
 and  $FF' = \frac{(TT')(OF)}{OT}$ .

# GEOMETRY

The error introduced by imprecise centering is determined by geometric principles (Fig. 1).

The following principles should be noted:

I. The smaller the target centering error,

† Chief Radiologist, Los Angeles County Harbor General Hospital, and Associate Professor of Radiology in Residence, University of California.

‡ Supervising X-Ray Technician, Los Angeles County Harbor General Hospital.

<sup>\*</sup> From the Departments of Radiology of the Los Angeles County Harbor General Hospital, Torrance, California, and the University of California Medical Center, Los Angeles, California.

Table I

RELATION OF MEASUREMENT ERRORS (ME) TO TARGET CENTERING ERRORS (TCE) AND OBJECT FILM

DISTANCES USING A 40 INCH TARGET FILM DISTANCE

Marie Control of the					
A. Object Film Dist TCE	ance 1.5 Inches				
in inches	0.25	0.5	1.0	2.0	4.0
ME					
in inches	0.01	0.02	0.04	0.08	0.16
in mm.	0.125	0.25	0.5	I	2
*2×ME					
in inches	0.02	0.04	0.08	0.16	0.32
in mm.	0.25	0.5	I	2	4
B. Object Film Dist TCE	ance 3 Inches				
in inches	0.25	0.5	1.0	4.0	8.0
ME					
in inches	0.02	0.04	0.08	0.16	0.32
in mm.	0.25	0.5	1	2	4
*2×ME					
in inches	0.04	0.08	0.16	0.32	0.64
in mm.	0.5	I	2	4	8
C. Object Film Dist TCE	ance 5 Inches			·	
in inches	0.25	0.5	1.0	2.0	4.0
ME					
in inches	0.035	0.07	0.14	0.28	0.56
in mm.	0.44	0.87	1.75	3.5	7.0
*2×ME					
in inches	0.07	0.14	0.28	0.56	1.12
in mm.	0.88	1.75	3.5	7.0	14.0

<sup>\*</sup> This represents the total error if the target centering error is duplicated in the opposite direction.

the smaller the error. (The error may either magnify or minify.)

- 2. The smaller the object film distance (OFD), the smaller the error.
- 3. When either the object film distance or target centering error is zero, there will be no error.
- 4. The object film distance will be between 2 and 6 inches in most cases and cannot be reduced to zero.
- 5. An increase in the target film distance (TFD) will reduce the error.

- 6. Table I shows the relation between measurement errors, target centering errors, and object film distance.
- 7. Target centering errors made in opposite directions will produce measurement errors which must be added to obtain the total measuring error.

# SLIT SCANOGRAPHY

Slit scanography, by essentially limiting the x-ray beam in the direction of the measurement to the nondivergent central ray, effectively limits the target centering error.

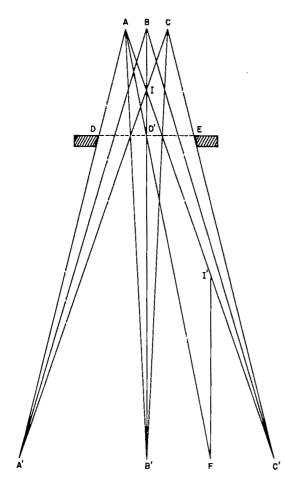


Fig. 2.

- (1) Points A, C, and B are points on the two lateral margins and the center of the target, respectively. Points A', C', and B' are points on the film or recording surface.
- (2) DE represents the collimator aperture.
- (3) Lines drawn connecting points A, B, and C with points A', B', and C' and from A to F represent the path of x-rays from the target to the film (A'C'). BB' is perpendicular to A'C'.
- (4) By inspection, it is apparent that the maximum divergence is with lines AC' and CA'.
- (5) The distance A'C' is 2 mm. and is obtained by adjustment of the aperture DE.
- (6) The intersection of the lines AC', BB', and CA' is labeled I. Let I represent a point in the object radiographed. An x-ray originating at point B and striking the film at B' would result in no distortion or magnification along the line A'C'. IB' is the object film distance.
- (7) The x-ray passing from AC' would magnify the image by the distance B'C'. This distance is by construction one half of A'C' or I

This provides a very high degree of accuracy which is not dependent upon the skill with which the technique is applied (Fig. 2).

mm. This represents the greatest error under conditions 4 and 5.

- (8) The location of I will vary with the ratio AC/A'C'. AC is the effective focal spot dimension in the axis of the table top movement. This will generally be 1 or 2 mm. with a 40 inch distance and a 1 mm. focal spot I will be 26.67 inches from A'C' and with a 2 mm. focus 20 inches.
- (9) It is apparent that the reference points in extremity length measurements will be much closer to the film and the object film distance will probably be not much more than 5 inches.
- (10) Let I' represent a point in an object closer to the film A'C' than I. A perpendicular is dropped from I' to A'C' at point F.
- (11) Triangle IB'C' is similar to triangle I'FC'.
- (12) Therefore:

$$\frac{FC'}{B'C'} = \frac{I'F}{IB'}.$$

(13) Consequently a reduction in the object film distance will result in a proportional reduction in the maximum possible measurement error. Since the maximum measurement error would be 1 mm. with a 2 mm. focal spot at 40 inch target film distance and a 20 inch object film distance, changing to a 5 inch object film distance would result in 0.25 mm. maximum error.

$$\frac{FC'}{I} = \frac{5}{20}$$
,  $FC' = \frac{5}{20} = 0.25$ .

(14) X-rays passing along line BB' would result in no magnification. X-rays would be evenly distributed on the film between points A' and C'. The average magnification will be the average of the maximum and minimum magnifications.

$$\frac{o + o.25 \text{ mm.}}{2}$$
 = 0.125 mm. average error.

(15) In view of this small magnification error and the higher tube loading imposed by the narrow slit, it might be preferable to use a wider slit and accept a greater error. As point I will rise as the ratio A'C'/AC is increased, doubling the slit with the same focal spot size will not quite double the magnification error and would reduce the tube load by one-half.

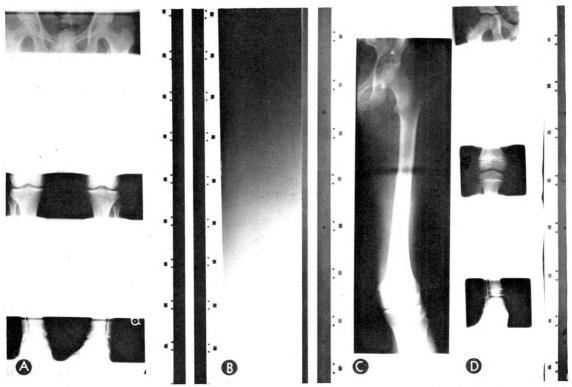


Fig. 3. The entire extremity to be measured may be radiographed or the points of interest only may be included. Measurements in all cases are made directly from the films.

A shows both hips, knees, and ankle joints on a single  $14 \times 36$  inch film; B shows the mask described in the text which is used to attenuate the light of the intensifying screens; C is a roentgenogram made with 2 such masks; and D is a  $36 \times 8$  inch roentgenogram showing one hip, knee, and ankle.

Special and costly apparatus have been constructed for this technique.3 Most departments do not have a sufficient demand for this procedure to warrant consideration of a special apparatus for this purpose. The usual mechanism provides for a tube movement during the exposure with a collimation of the x-ray beam to a narrow slit running perpendicular to the direction of the tube motion. The movement of the tube could be motorized or could be as simple as a rope and pulley pulled by hand.<sup>2</sup> A single long cassette would be placed beneath the patient parallel to the longitudinal axis of the table top and measurements can be made directly from the film with no requirement for correction. Ideally there should also be a provision for modifying the exposure technique with changes in the thickness of the part.

# OUR TECHNIQUE

Our technique does not differ in principle from slit scanography as described above. The principal difference is the use of a remotely operated moving table top to move the patient and cassette while the tube remains stationary.

Depending on the requirements, there are several variations in the technique. These are:

1. Exposing the film only over the reference points of interest, *i.e.*, over the femoral head and knee, femoral head and ankle or femoral head, knee, and ankle (Fig. 3,  $\mathcal{A}$  and  $\mathcal{D}$ ). This has the advantage of reducing the patient radiation exposure and permits an easy adjustment of exposure technique between the separate exposures to compensate for differences in the part thick-

nesses. This also imposes a lower tube burden than a continuous exposure.

- 2. Radiographing both legs on one 14 inch  $\times$  36 inch film (Fig. 3A).
- 3. A continuous exposure demonstrating the entire part to be measured on the film (Fig. 3C). The achievement of proper density could be provided by a continuous voltage or milliamperage control or by a variation in table top speed. Since none of these options was readily available we used specially prepared x-ray film to selectively attenuate the light from the intensifying screens. These were prepared by using a wedge filter and exposing several 8 inch × 36 inch films. The films thus prepared were dark grey at one end and became progressively lighter as the other or clear end was approached (Fig. 3B). It was found necessary to reduce the light from both screens by placing the unexposed film between two such film masks, with the denser end oriented towards the thinner part of the patient. The density ranges required in such masks would obviously vary with the relationship between the maximum and minimum dimensions of the part to be examined.
- 4. Radiographing each leg separately on an 8 inch  $\times$  36 inch cassette (Fig. 3D).

The slit collimation can be provided by a diaphragm. This has the advantage of providing a precise slit width. This is important as the exposure technique varies inversely as the slit width. We have found it satisfactory to narrow the slit to a 2 mm. width on the table top by means of the light visualizer of a Siemens collimator.

The width of the diaphragm slit can be calculated by the following formula (Fig. 2):

Diaphragm slit width = DE Target film distance = BB' Diaphragm target distance = BD' Slit width at the film level = A'C'

$$\mathrm{DE} = \frac{\mathrm{A'C'(BD')}}{\mathrm{BB'}}$$

## TABLE II

Technical Factors

Target film distance 40 inches Slit width at film level 2 mm. Screens Mid Speed Film DuPont Cronex II No grid or Bucky diaphragm Focal spot 2 mm. 100 milliamperes

Continuous Exposure

Exposure begun about 5 cm. above proximal measurement point and continued to about 5 cm. below distal measurement point

Length of exposure is determined by length to be measured

Our table top moves about 2 inches per second. Kilovoltage 70-75.

Compensating film masks used to even radiographic density between thin and thick parts.

Discontinuous Exposure

Exposure begun about 5 cm. above point to be measured and continued to 5 cm. below this point, then moved to next point and repeated Exposure time 2 seconds

Kilovoltage

Hip 72-77 Knee 56-60 Ankle 45-50

This treats the focal spot as a point. The small error thus introduced is not considered significant.

It is recognized that the similarity of x-ray and light beam collimations are frequently not precise. In practice, this approximation has been close enough both from the technical factors and magnification error aspects.

The cassette is placed on the table top, parallel with the long axis of the table, and the part to be measured is placed in position parallel with and on the cassette. When the table top is moved, the part, film, and table top position must remain unchanged. We have found non-Bucky films satisfactory. A stationary grid could be used for the thicker parts but tube loadings would be higher.

The table top movement is actuated by the x-ray technician just before making the x-ray exposure. The initial position of the

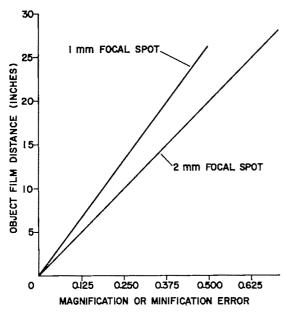


Fig. 4. Graph showing the minor part played by focal spot size in the measurement error.

slit is above the point of reference and movement is continued until the point of reference is passed with certainty. Our table top moves with a velocity of about 2 inches/second. The exposure technique requirements vary directly with table top velocity.

Table II gives some typical exposure techniques.

# MEASUREMENTS

After processing, the measurements are made without correction directly from the film. We have found the measurements to be consistent and reproducible in an experience of about two dozen examinations in the past year.

Figure 4 shows the maximum distortion at different object film distances.

#### CONCLUSIONS

- 1. Longitudinal table top motion, a slit diaphragm or collimator plus a long cassette are items of equipment available in many radiology departments. These items may be used to measure extremities in a very accurate and reproducible slit scanography method. The error is calculated to be  $\pm 0.125$  mm. (Fig. 2).
- 2. The precision of this method is not dependent on the skill of the technician but lies in the method.
- 3. A method for variable attenuation of the emission of light from intensifying screens to compensate for differences in part thickness is described.

John H. Woodruff, Jr., M.D. UCLA Medical School Los Angeles, California 90024

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# PATHOLOGIC STUDIES FOLLOWING MAGNETIC CONTROL OF METALLIC IRON PARTICLES IN THE LYMPHATIC AND VASCULAR SYSTEM OF DOGS AS A CONTRAST AND ISOTOPIC AGENT\*

By PHILLIP H. MEYERS, M.D.,¹ CHARLES M. NICE, Jr., M.D., Ph.D.,² GEORGE R. MECKSTROTH, Ph.D.,³ HAL C. BECKER, M.S.,⁴ PHYLLIS J. MOSER, B.A., R.T.,⁵ and MELVIN GOLDSTEIN, M.S.º NEW ORLEANS, LOUISIANA

EXPERIMENTAL studies were designed to determine the distribution and pathologic effect of metallic iron particles in the tissues of experimental animals, and to demonstrate whether the radioactive and nonradioactive iron particles can be magnetically controlled in vivo in the veins, arteries, lymph channels, and gastrointestinal tract of experimental animals.

# MATERIALS AND METHODS

Carbonyl iron particles 1-3 microns in size were used in these experiments. A very pure form of commercial iron, carbonyl iron, is produced by allowing carbon monoxide gas to pass over sponge iron at suitable temperatures and pressures, forming an iron carbonyl which is liquid at room temperature. The iron carbonyl decomposes to form again both the metal and carbon monoxide at higher temperatures and atmospheric pressure. Iron produced from iron carbonyl is nearly pure, containing less than 0.0007 per cent carbon and less than 0.01 per cent oxygen. The relative purity of this form of iron makes it ideally suited for the manufacture of magnetic cores.

Fifteen grams of carbonyl iron particles,

1-3  $\mu$  in size, were suspended in 5 gm. of 360,000 molecular weight polyvinylpyrolidine dissolved in 20 cc. of water and used as intravenous injections in 28 dogs. The radiopaque iron particles were held in situ with an externally placed electromagnetic system of approximately 2,000 gauss strength. Conventional roentgenograms were taken to visualize the intravenously held particles. After the particles were released from the magnetic field and the injection site massaged, the iron was no longer visualized.

With a suspension of corn syrup (200 cc.) and 10 grams of micronized carbonyl iron, gastrointestinal studies were carried out in 15 dogs by passing the solution through a tube into the esophagus. The radiopaque particles were held in place by the externally placed magnets, resulting in a controlled esophagram and a controlled visualization of the upper gastrointestinal tract, small intestine, and colon (Fig. 1 and 2). After release of the magnetic field, the iron suspension was allowed to flow into the lower gastrointestinal tract; here a controlled roentgenogram was possible, with the magnetic field on again. A similar observation was made by injecting the mi-

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<sup>&</sup>lt;sup>1</sup> Associate Professor, Department of Radiology, Tulane University School of Medicine, New Orleans, Louisiana. <sup>2</sup> Professor and Chairman, Department of Radiology, Tulane University School of Medicine, New Orleans, Louisiana; Director of Diagnostic Radiology, Charity Hospital, New Orleans, Louisiana.

Assistant Professor of Radiology (Physics), Tulane University School of Medicine, New Orleans, Louisiana.
Associate Professor of Biomedical Engineering (Radiology), Tulane University School of Medicine, New Orleans, Louisiana.

Research Coordinator, Registered Nuclear Medicine Technologist, (ARRT), Department of Radiology, Tulane University School of Medicine, New Orleans, Louisians.

<sup>&</sup>lt;sup>6</sup> Physicist; President, Technical Associates of New Orleans, Louisiana.

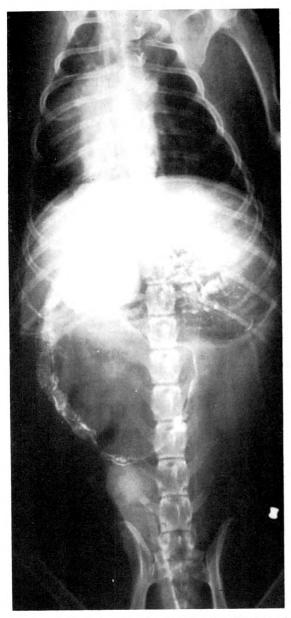


Fig. 1. Roentgenogram showing the distribution of 10 grams of micronized iron admixed with 200 cc. of corn syrup before a magnetic field is applied.

cronized iron directly into the right ventricle of the heart (Fig. 3).

Two to five gram single injections of radioactive micronized carbonyl iron (50–100  $\mu$ c Fe<sup>59</sup>) were used to trace the deposition of the particles through the dogs' systems. *In vivo* (Fig. 4) and *in vitro* (Table 1) counting demonstrated that the liver, spleen, pancreas, kidneys and heart,

in that order, contained the most activity. The greatest part of the intravenously injected radioactive iron was excreted through the kidneys (Fig. 5).

The blood picture of each experimental dog was noted at the beginning of each study and periodically tested throughout the course of the study. Blood urea nitrogen levels were also monitored regularly, and urine specimens were analyzed microscopically (Table II and III).



Fig. 2. Roentgenogram showing micronized iron under magnetic control in the small bowel and stomach. Note that the particles line up according to the magnetic field force even though they are not between the pole pieces.

Desferrioxamine B, a chelating agent found to remove rapidly abnormal amounts of iron in the human system, was introduced intravenously into several of the experimental animals to contrast the time removal of the iron particles from those dogs who had received the chelate with the removal time from those who had not (Fig. 6).

# RESULTS

In dogs which were injected with 2-5 grams of iron particles, the findings of radioactive iron particles in the liver, spleen, pancreas, kidneys, and heart, respectively, were substantiated by histologic investigations in which cells of these organs contained irregularly shaped particles of various sizes showing a positive iron stain. Histologically, iron particles were found in the largest quantity in macrophages in the liver and spleen. Many Kupffer's cells lining the sinusoids of the liver contained irregular particles of various sizes showing a positive iron stain. These particles were readily differentiated from hemosiderin by differences in morphology. Nodular aggregates of Kupffer's cells were quite fre-

Table I A comparison of in vitro counts in acute and chronic dogs receiving 50  $\mu c$  Fe<sup>59</sup> carbonyl iron powder intravenously

0	Ac	ute	Chronic		
Organ	СРМ	μς	СРМ	μς	
Spleen	3,277	.0113	618	.002	
Pancreas	60	.0002	183	.0006	
Kidneys	646	.0022	735	.0025	
Liver	2,714	.0094	1,580	.0054	
Lungs	8,450	.0292	370	.0013	
Heart	600	.002	911	.003	

A comparison of *in vitro* counts in acute (3 days) and chronic (77 days) dogs receiving 50  $\mu c$  Fe<sup>59</sup> carbonyl iron powder intravenously showing that liver and spleen still have consistently the highest count in both acute and chronic dogs. This would be expected since this is part of the reticuloendothelial system. Note that in the chronic dog there is a small increase in counts of the heart tissue and a marked decrease in the counts of lung tissue. This is most likely explained on the basis of embolization which occurred in dogs receiving large intravenous injections of iron, due to the lack of demagnetization.



Fig. 3. Roentgenogram demonstrates a gross experiment after injecting 10 grams of micronized iron directly into the right ventricle. We were able to retain the iron within the magnetic field of approximately 1,350 gauss. This magnetic field force was sufficient to prevent the blood flow from removing the iron particles.

quently found in localized regions of the sinusoids. These aggregates were also sporadically situated in the lobules. Occasional macrophages containing iron particles were present in the stroma of the portal triads. The spleen showed many macrophages containing iron particles of various dimensions, principally situated in the red pulp. The lungs showed the least amount of total iron, estimated from the multiple sections taken from this organ. Fairly frequent small emboli composed of

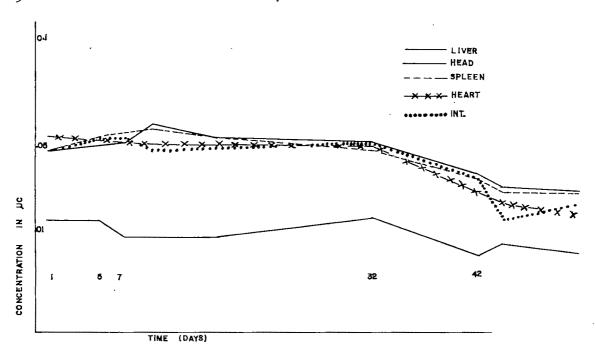


Fig. 4. In vivo counts on a typical dog receiving 100  $\mu$ c carbonyl micronized iron intravenously and followed for 6 weeks, showing greatest concentration of iron to be in the liver and spleen.

iron particles were found in slightly ectatic portions of the capillaries in the alveolar wall. Emboli were present only rarely in the arterioles. However, there were no lesions in the small, medium or large sized arteries. Occasional macrophages containing fine particles of iron were present in the areolar tissue adjacent to the bronchioles.

In contrast, the dogs receiving larger amounts of iron particles (10-15 grams,

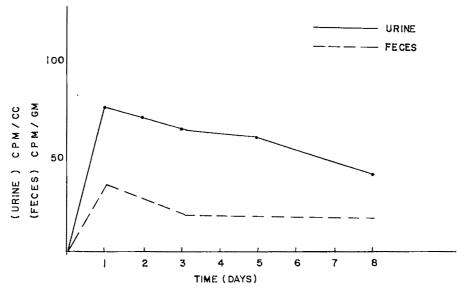


Fig. 5. Graph showing the gradual excretion via feces and urine of 50  $\mu$ c Feb radioactivity given intravenously to a typical dog with no chelating agent, indicating that most of the intravenously injected radioactive iron is excreted through the kidneys.

both magnetized and unmagnetized) had large embolic masses of iron particles occluding large and medium sized arteries; occasional small arteries were also occluded. In addition, there were frequent small capillary emboli and extensive pulmonary edema and congestion. In some of these same dogs who received larger injections of carbonyl iron, especially those who had been magnetized, many medium and small sized arteries showed iron particles in "organizing" emboli. These polypoid intraluminal embolic lesions were composed of aggregates of iron particles situated in sheets of macrophages. Almost all of the reactive cells were macrophages with the exception of endothelial cells forming the covering over these lesions.

For the most part, other organs rarely showed significant embolic lesions. The kidneys showed occasional small emboli in the peritubular plexus and in the thin

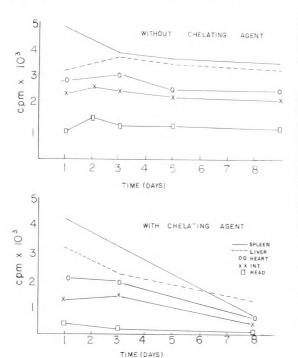


Fig. 6. Two graphs comparing the excretion of iron particles *in vivo* in 2 dogs, 1 of which received a chelating agent to hasten the excretion. Desferrioxamine B (250 mg.) was injected intramuscularly daily for 4 days. The graphs show that the chelate greatly increased the excretion of particles.



Fig. 7. Photograph showing the breadboard of the electronic circuitry for generating static and oscillating magnetic fields. The major components of the system are: (1) a variable frequency and amplitude oscillator, (2) a variable DC±supply, (3) an operational amplifier, (4) a power amplifier, and (5) wire coils.

walled vessels of the medulla. Rare macrophages containing iron particles were present in the submucosa of the small bowel. Tissues taken from the injection site in the

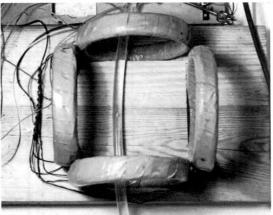


Fig. 8. A static magnetic field is generated on one axis while an oscillating magnetic field (transverse to the static field) is generated on the other. The static field determines the orientation of the drone, while the oscillating field will generate a "swimming" action. By appropriately shaping the drone, a differential pressure which propels the drone is generated during the "swim." Note the drone (seen as a small opacity) within the plastic tubing.

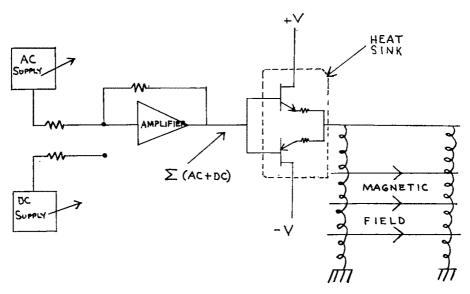


Fig. 9. Simplified circuit for one axis of the prototype drone system.

dogs' forelegs showed moderately sized aggregates of macrophages containing iron particles present in the adjacent dermis. One animal showed extensive ulceration and a necrotizing phlebitis at the injection site.

The red blood cell count, hemoglobin and hematocrit values obtained in dog blood tests were steady and normal; the white blood cell count rose significantly and sharply after the injection of iron particles intravenously. Ten dogs under a long

term study returned to a normal white blood cell count at the end of 6 weeks. Blood urea nitrogen levels were within normal range throughout the studies, showing no change for either the intravenously injected group or the gavaged group (Table II and III). The *in vitro* counts of radioactivity per organs in a chronic dog are given in Table IV. The *in vivo* values of serum iron, iron binding capacity, and total iron binding capacity are listed in Table V. Histologic studies of renal tissue indicated

Table II Laboratory work on chronic study of dog receiving 100  $\mu c$  Fe<sup>59</sup> carbonyl iron intravenously

	May 13	May 27	June 3	July 6	July 16	July 23	August 25
Blood Study							
Red blood cells	6,9∞0,∞∞	5,640,000	4,700,000	5,140,000	5,610,000	6,270,000	7,020,000
Hemoglobin (gm.)	11.8	11.8	12.5	11.8	15.2	13.6	15.6
Hematocrit (%)	35	34	34	36	41	40	47
White blood cells	10,950	11,500	15,900	8,750	13,300	9,850	6,700
Blood urea nitrogen			•	7,-			•
(mg.)	14.8	13.0	14.8	16.8	16.0		15.8
Urinalysis							
Leukocytes	I		3-4	2-3	3-4	1	I
(per high power field)				-	1		
Casts	r-2			1-3	F		
(per high power field)				•			

Laboratory work on a typical chronic dog receiving 10 grams intravenously of carbonyl iron containing 100  $\mu$ C Fe<sup>50</sup> showing a rise of white blood cell count following injection of iron particles with a gradual decline over a period of months. Urinalysis showed some infection in the system which gradually cleared. Other laboratory data remained within normal limits for laboratory dogs. The data on 5–13 represent laboratory values before injection.

Table III
LABORATORY WORK ON CHRONIC DOG RECEIVING 50 GM. CARBONYL IRON PER
GAVAGE INTO UPPER GASTROINTESTINAL TRACT

	July 1	July 11	July 20	August 12	August 27
Blood Study Red blood cells Hemoglobin (gm.) Hematocrit (%) White blood cells Blood urea nitrogen (mg.)	5,870,∞0 12.6 45 4,550 14.8	5,590,∞0 11.3 35 9,450 7.8	6,050,000 12.2 35 17,800 15.0	6,250,000 12.4 34 15,400 16.0	6,4∞,∞ 12.2 38 13,2∞ 16.2
Urinalysis Leukocytes (per high power field) Casts (per high power field)	1-3 3-4	3-4	I-2	I-2 O	0

Laboratory work on a dog which received 50 gm, carbonyl iron into the upper gastrointestinal tract. The iron in the stomach of this dog was controlled magnetically and drawn into the mucous lining of the stomach with magnetic force, causing some irritation and the resulting white blood cell count rise. The dog also had some urinary infection.

that there were only rare embolic regions in the kidneys.

Those dogs which were injected additionally with the chelating agent demonstrated, by means of daily in vivo counting, that the chelate, desferrioxamine B (supplied as Ciba's Desferal) did hasten the excretion of the particles via urine and feces.

# DISCUSSION

In our radiologic research laboratories, we have been determining the strength of the magnetic field necessary to hold iron particles in specific locations in the gastro-intestinal tract in the varying body widths or thicknesses of experimental animals. We have been able to control the iron contrast material in the gastrointestinal tract and hold it in specific places for as long as we desire.

For purposes of our discussion, we define acute studies as those in which the experimental animals were sacrificed at times varying from immediately after the procedure to 3 days later. Long term study animals are those which were sacrificed 3 weeks, 6 weeks, 3 months, 6 months and 9 months following the experimental procedure; 5 animals are living I year following the injection or ingestion of iron particles.

Our acute toxicity and long term toxocity pathologic studies indicate so far that there are no gross deleterious effects of the metallic iron particles used under magnetic control as a contrast agent in the gastrointestinal tract, so long as the magnetic field force does not pull the iron particles into the mucosa of the gastrointestinal tract. Radioactive iron studies also indicate no evidence of any gross injurious effects of magnetic iron in the sites of localization.

We are just beginning to learn how to degauss or demagnetize the iron particles

TABLE IV

in vitro counts of chronic dog receiving 25 gm. (50 µc) carbonyl iron powder per gavage into gastrointestinal tract and sacrificed 77 days after experiment

	cpm	μς
Kidneys	696	.0024
Lungs	696 617	.0021
Spleen	31	.0001
Heart	133	.0004
Liver	150	.0004 .0005

These are in vitro counts per minute for each organ system and the total number of  $\mu c$  in each organ system of a dog sacrificed 77 days after a study in which he received 25 gm, of carbonyl iron containing 50  $\mu c$  Fe<sup>55</sup> into the upper gastrointestinal tract. The typical dog regurgitated part of the suspension into the lungs. This most likely explains the counts in the lung tissues and kidneys.

Table V

EXAMPLE OF LABORATORY VALUES IN TYPICAL CHRONIC DOGS RECEIVING CARBONYL IRON PARTICLES BY INTRAVENOUS INJECTION (10 GM.)\*

	Dog A Dog B		Dog C	
Serum iron Iron binding capacity	130 gm./% 200 gm./%	95 gm./% 200 gm./%	120 gm./% 210 gm./%	
Total iron binding capacity	330 gm./%	295 gm./%	330 gm./%	

<sup>\*</sup> Normal laboratory values: Serum iron = 80-180 gm./%. Total iron binding = 300-350 gm./%.

EXAMPLE OF LABORATORY VALUES IN TYPICAL CHRONIC DOGS RECEIVING CARBONYL IRON PARTICLES IN THE GASTROINTESTINAL TRACT BY GAVAGE (50 GM.)\*

	Dog 1	Dog 2	
Serum iron Iron binding capacity Total iron binding capacity	115 gm./% 233 gm./% 348 gm./%	130 gm./% 210 gm./% 340 gm./%	

<sup>\*</sup> Normal laboratory values: Serum iron = 80-180 gm./%. Total iron binding = 300-350 gm./%.

(after they have once been magnetized) with pulsating alternating fields.

Our experiments have demonstrated that we must have electromagnetic systems in which the magnetic fields can be delicately and precisely controlled. These magnetic control systems have been described by Professors E. H. Frei and S. Leibinzohn<sup>8,5</sup> of the Department of Electronics, The Weizmann Institute of Science, Rehovoth, Israel. Therefore, we have completed and tested a prototype drone device (as shown in Fig. 7-9), i.e., a simple miniature device that can be propelled and guided in the vascular system by a magnetic field. Nearing completion is a magnetic control system that will completely enclose an experimental animal in a 360° magnetic field. We hope to control the path of a 2 mm. by I mm. drone of very high magnetic material such as platinum cobalt (high dipole) within the vascular system of the experimental animals.

Recently Fingerhut and Alksne<sup>2</sup> developed a simple method of thrombosing aneurysms using externally placed magnets and intra-arterially injected iron particles, experimentally in dogs.

#### CONCLUSION

A group of radiologists, physicists, and biomedical engineers designing and constructing the above described drone system theorize that a miniature catheter attached to a remotely-controlled drone can be inserted into any blood vessel the size of the drone. We hope to have this system in experimental operation within 6 months. Our experiments will then proceed toward the conceptional idea of developing this system into the following medical applications: (1) biopsy device, (2) release of chemicals in specific locations, (3) suction of blood clots, (4) chemical dissolution of blood clots, (5) contrast media injection, (6) measuring devices, and (7) sampling devices.

Phillip H. Meyers, M.D. Department of Radiology Tulane University School of Medicine New Orleans, Louisiana

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# CINEROENTGENOGRAPHIC OBSERVATIONS OF THE CRICOPHARYNGEUS\*

By WILLIAM B. SEAMAN, M.D. NEW YORK, NEW YORK

HERE is still no consensus as to the 1 clinical significance of a posterior indentation of the barium bolus at the pharyngoesophageal junction. Although variously referred to as the hypopharyngeal bar, esophageal lip, spasm or hypertrophy of the cricopharyngeus, most authors agree with Templeton and Kredel<sup>22</sup> that it is produced by the cricopharyngeus muscle. Crichlow<sup>5</sup> emphatically states that this bulge is never seen in the normal and represents evidence of dysfunction when it is visualized. Johnstone<sup>12</sup> considered it of no definite pathologic significance since it occurs in patients without symptoms. Siebert et al.20 stated that the smaller indentations were not significant although none of her patients was symptomatic. Others<sup>19,21</sup> hold to the opinion that the visualization of the cricopharyngeus indicates the presence of muscular spasm or hypertrophy.

Since the introduction of cineroentgenographic techniques for routine gastrointestinal examinations several years ago, we have encountered some form of cricopharyngeal indentation in approximately 5 per cent of all patients examined. I fully agree with Crichlow that the cricopharyngeus is not seen in the normal. It is also true that this phenomenon may occur in patients without definite symptoms relating to swallowing. However, in my opinion, the appearance of the cricopharyngeal indentation is reliable evidence of the presence of neuromuscular dysfunction of the swallowing act. The absence of symptoms is an unreliable criterion for the normality of swallowing. Over a period of time, many patients with abnormalities of deglutition become conditioned to swallowing slowly and carefully and have acquired

dietetic limitations which become auto-

#### ANATOMY

The cricopharyngeus according to Killian<sup>18</sup> consists of two parts: a pars obliqua and a pars fundiformis or transverse portion. The oblique fibers arise from the posterior portion of the lower third of the lateral surface of the cricoid cartilage and sweep back and up to insert into a median raphe common to the other pharyngeal constrictors. They fuse intimately with the fibers of the inferior pharyngeal constrictors and have an identical function. The transverse fibers also arise from the lateral margins of the cricoid cartilage but pass horizontally backwards without interlinking dorsally in a raphe, forming a sphincter. These fibers are easily separated from the oblique portion, leaving a potentially weak spot, which is called Killian's dehiscence or the triangle of Lannier. It is here that the Zenker diverticulum arises. This horizontal band of fibers measures about IC-I2 mm. in height and is responsible, together with the uppermost bundle of the esophageal circular muscle, for the closure of the mouth of the esophagus.

It is important to emphazise that anatomic variations do occur since some confusion has arisen regarding the circular fibers of the cricopharyngeus and those of the esophagus. In the instance when the circular fibers of the cricopharyngeus are scanty or absent and those of the esophagus well developed, such confusion is understandable. Perrott, <sup>18</sup> after dissecting 40 cadavers, found 40 per cent in which there were very poorly developed circular or lower fibers of the cricopharyngeus and an additional 30

<sup>\*</sup> From the Department of Radiology, College of Physicians and Surgeons, Columbia University, and Columbia-Presbyterian Medical Center, New York, New York.

per cent in which no definite demarcation between circular and oblique fibers could be found; but in no case were any of the muscular fibers of the esophagus demonstrated to be microscopically continuous with the lower fibers of the cricopharyngeus. The outer longitudinal muscular canal of the esophagus is over-lapped by the circular fibers of the cricopharyngeus but quite separate from them. The transverse or circular fibers of the esophagus lie deep to the longitudinal muscle bundles.

# PHYSIOLOGY

In the resting state, the upper end of the esophagus is closed by the tonic contraction of the cricopharyngeus. This sphincter arrangement is essential for pulmonary respiration by negative pressure and prevents air from entering the esophagus. The presence of a high resting tone has been confirmed by manometric studies which have demonstrated a band of elevated pressure between the pharynx and esophagus.<sup>3,4,7</sup> During deglutition, this sphincter opens immediately upon the entry of a bolus into the pharynx before maximal contraction of the pharyngeal constrictors but after the larynx has started to move upwards. This is accompanied by a negative pressure in this region while a positive pressure of up to 100 cm. of water develops in the pharynx above. This manometric evidence supports the view that the cricopharyngeus and probably some of the adjacent circular muscles of the esophagus are in a state of tonic contraction during resting conditions and that this contraction is actively inhibited during the act of swallowing. It normally remains in a relaxed state for .5 to 1.2 seconds.

In closing, the intraluminal pressure in the region of the cricopharyngeus transiently exceeds that of the resting phase, a manifestation of the peristaltic sequence. That such a phenomenon, characterized by split second timing, should be subject to disorders of coordination, is not surprising. The bolus does not actively distend the sphincter; the inhibition of the normal



Fig. 1. Normal pharynx and proximal esophagus distended with barium. Note smooth contour of the posterior wall.

resting tone anticipates the arrival of the bolus. It seems evident that failure of the cricopharyngeus muscle to open completely or its premature closure would permit it to intrude into the passing barium bolus and produce a posterior indentation. It does not seem necessary, in the presence of the sphincteric bulge, to postulate the existence of spasm or hypertrophy, since it can be more easily explained by the partial failure of the normal wave of inhibition or a lack of precise synchronization with the other phenomena of deglutition.

# ROENTGENOGRAPHIC APPEARANCE

In the normal patient the fully distended pharynx has a smooth posterior wall (Fig. 1). The roentgenographic manifestations of the cricopharyngeus range from a minimal protrusion into the tail of the passing bolus to a horizontal shelf that completely occludes the lumen. Its shape may also be hemispherical or triangular (Fig. 2; and 3B). Both Crichlow,5 and Siebert et al.,20 have quantitated the degree of indentation into 4 stages. In its mildest and most frequent manifestation, it merely seems to pinch off the tail of the barium bolus. In other patients it may appear during the period of maximum distention of the pharynx for about one-tenth of a second and then dis-



Fig. 2. Cricopharyngeal impression having a hemispherical configuration.

<del>\ \\\\</del>

appear. Thus, in using cineroentgenographic techniques at 12 frames per second, it may only appear on one frame (Fig. 3, A B and C). This undoubtedly explains its greater incidence in cineroentgenography and the difficulty in observing it during conventional fluoroscopy and spot roentgenography.

Although its incidence increases with advancing age, it is not unknown in infants. Its demonstration in a six month old infant (Fig. 4) following the repair of a tracheoesophageal fistula supports the contention

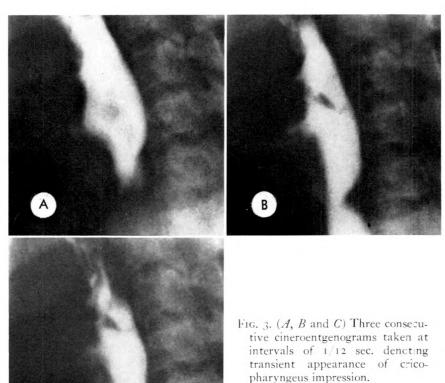




Fig. 4. Prominent cricopharyngeus in a 6 month old infant following repair of tracheo-esophageal fistula.

that its presence is a manifestation of neuromuscular dysfunction, since Kirk-patrick *et al.*<sup>15</sup> have demonstrated abnormal motor activity of the esophagus in 15 patients operated on for esophageal atresia.

The cricopharyngeal impression becomes particularly prominent after total laryngectomy. Schobinger<sup>19</sup> reported 10 of 42 patients subjected to total laryngectomy who developed severe dysphagia and a prominent cricopharyngeus. In most instances the degree of prominence of the crico-



Fig. 6. Carcinoma of the proximal esophagus simulating a prominent cricopharyngeus. The differentiation from a cricopharyngeus impression is based on the persistence of this configuration.

pharyngeal impression correlated with the severity of the dysphagia. He attributed the dysphagia to cricopharyngeal spasm. The cricopharyngeus and inferior pharyngeal constrictor muscles are detached from the cricoid and hyoid during surgery and tend to bunch posteriorly when a nerve impulse reaches them, since they lack an anterior attachment. In our experience a prominent cricopharyngeus is more fre-

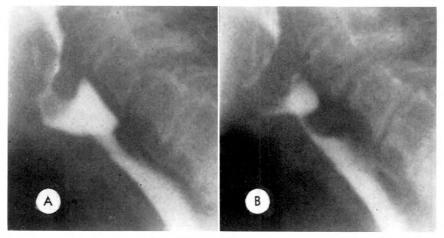


Fig. 5. (A) Prominent cricopharyngeal impression after total laryngectomy. Note deep indentation above due to compensatory hyperactivity of the pharyngeal constrictor. (B) The contraction wave of the pharyngeal constrictor has moved down to the cricopharyngeus producing a pseudodiverticulum.

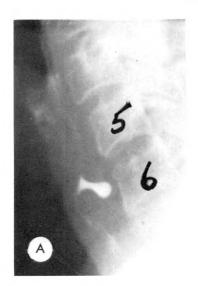
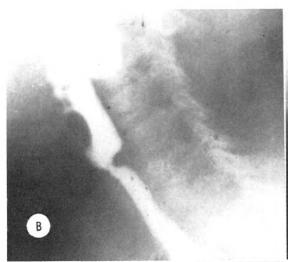
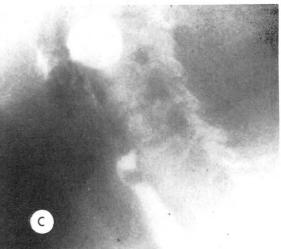


Fig. 7. (A) Conventional lateral spot roentgenogram of the neck after a barium swallow disclosing a small diverticulum.



quent in laryngectomized patients, but not as frequent as Schobinger reports and not necessarily associated with symptoms. This may be related to the surgical technique employed. According to Kirchner *et al.*, <sup>14</sup> interference with pharyngeal peristalsis is probably responsible for the dysphagia after laryngectomy.





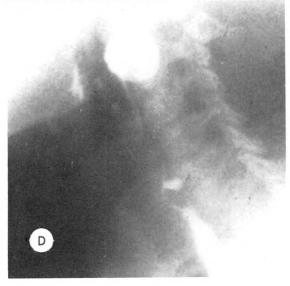
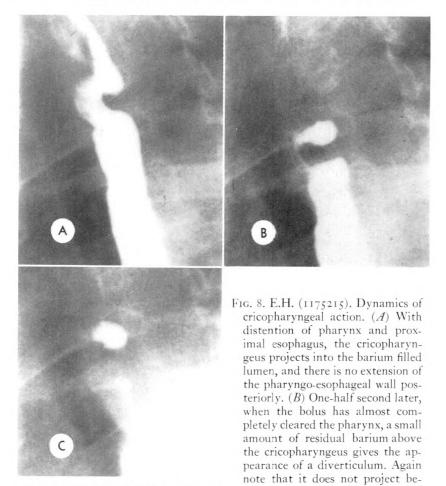


Fig. 7. (B, C and D) Selected frames from the cineroentgenographic examination of the same patient showing that, when the esophago-pharynx is fully distended, no diverticulum is visible, only a prominent cricopharyngeus.



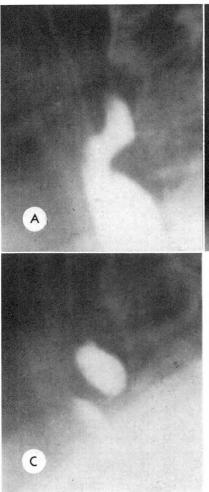
yond the normal limits of the posterior esophageal wall. (C) Bolus has completely cleared the pharynx leaving only a pseudodiverticulum.

Hyperactive peristalsis in the pharynx, probably of a compensatory character, may produce a posterior indentation similar to that caused by the cricopharyngeus but at a higher level. Serial roentgenograms demonstrate that these peristaltic constrictions move down and finally merge with the cricopharyngeal indentation (Fig. 5, A and B).

The shape and the characteristic transience of the cricopharyngeus indentation usually make it easy to differentiate from benign or malignant tumors. One patient with a carcinoma in this area simulated the prominent cricopharyngeus (Fig. 6), but the constancy and lobulated contour of the neoplasm facilitated the differential diagnosis.

POSSIBLE RELATIONSHIPS BETWEEN A
PROMINENT CRICOPHARYNGEUS MUSCLE
AND THE DEVELOPMENT OF A POSTERIOR
PHARYNGEAL DIVERTICULUM

The appearance of a prominent cricopharyngeus muscle may change during the various stages of swallowing and at a certain phase, may resemble a small diverticulum (Fig. 7, A-D; and 8, A,B and C). A residual collection of barium on the superior surface of the cricopharyngeus muscle seems to project posteriorly and form a small pouch. However, serial analysis of cineroentgenographic studies reveals that during maximum distention of the pharynx and proximal esophagus, the posterior projection seems to disappear and the appearance becomes that of a horizontal shelf



B

Fig. 9. Variable appearance of a small Zenker diverticulum.

(A) In this phase only a prominent cricopharyngeus muscle is visible. (B) Appearance of small diverticulum projecting posteriorly.

(C) After the bolus has passed, the pouch is distended with residual barium.

projecting into the lumen, compatible with a prominent cricopharyngeal impression.

In 1932, Gray<sup>8</sup> noted a posterior projection, 3 to 4 mm. in depth, arising from the posterior pharyngeal wall at the level of the cricoid cartilage. Its position and shape suggested to Grav that this was due to herniation of pharvngeal mucosa between the circular and oblique fibers of the cricopharyngeus muscle. He observed that the projection became visible only after the main part of the bolus had passed and that no abnormality could be seen while the bolus was actually passing from the pharynx into the esophagus. In our experience, the latter is only true in the case of smaller projections; in others, as noted above, during the passage of the main bolus, a cricopharyngeus impression is still visible. Grav observed these phenomena in 16 patients and considered them as unstable diverticula that would probably develop into a true Zenker's pouch. Holmgren, 10,11 14 vears later, reported 18 additional examples of this condition; six of which were followed for  $4\frac{1}{2}$  years without increasing in size or becoming a Zenker's diverticulum. He explained the phenomenon as being due to the development of a negative pressure behind the posterior hypopharyngeal wall because of contraction of the pharyngeal muscles and an increase of pressure within the hypopharynx. He felt that if nonstable diverticula of the hypopharynx are capable of developing into Zenker's diverticula, many do not do so, since he observed an incidence of 45 per cent of such diverticula

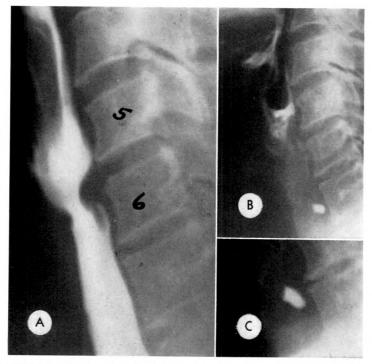


Fig. 10. Eight year follow-up of a prominent cricopharyngeus impression and pseudodiverticulum. (A) Distended pharynx and esophagus demonstrate a typical cricopharyngeus indentation. (B) Residual barium on the superior surface of the cricopharyngeus simulates a diverticulum. (C) Similar appearance 4 years later.

in patients over 50 as compared to a 2 per cent incidence of true Zenker's diverticula in the same age group.

More recently Sutherland<sup>21</sup> described a similar pouch that exhibited no change during a 5 year period of observation and disappeared following a vertical extramucosal myotomy of the cricopharyngeus. We have only had the opportunity to make one long-term follow-up. This patient was examined on 3 occasions over a period of 8 years but no significant change was noted (Fig. 10, A-D). We are inclined to agree with Holmgren that if these small pouches are precursors of a true Zenker's diverticulum, their metamorphosis is probably a slow process. We have seen forms that seem to represent a transitional stage between a prominent cricopharyngeus and a true diverticulum (Fig. 8, A, B and C; and 9, A, B and C), but, as yet, we have not been able to document the transition in the same individual.

According to Negus, 17 neuromuscular

dysfunction in the second stage of swallowing is the etiologic factor in the production of Zenker's diverticula. Peristaltic activity



Fig. 10. (D) Frame from a cineroentgenographic examination 8 years later showing no change.

by the pharyngeal constrictors associated with defective inhibition of the resting tone of the cricopharyngeus results in an abnormally high pressure being exerted against the unprotected area between the horizontal fibers of the cricopharyngeus and the oblique fibers of the inferior pharyngeal constrictor. Negus states that, if this is true, the diverticulum is a consequence of dysphagia caused by deficient muscular relaxation and is not, at least in its initial stage, the cause of the dysphagia. In accord with this theory is the relief afforded to some patients, by the performance of a cricopharyngeal myotomy. Negus also described a patient in whom dysphagia persisted after removal of the diverticulum. Roentgenographic examination showed a prominent cricopharyngeus bulge, and dilatation of the esophagus was required to correct the disorder. Ardran and Kemp<sup>1</sup> make this statement concerning pharyngeal diverticula, "The cause is clearly due to deranged function of the pharyngeal constrictors: the cricopharyngeus closes partly or completely before the whole of the bolus has been displaced from the pharynx and the contraction of the pharyngeal musculature upon the body of the bolus causes the protrusion to appear."

# SUMMARY

The posterior indentation of the barium column of the pharyngoesophageal junction, which can be observed in 4 to 5 per cent of cineroentgenographic examinations of this area, is produced by the cricopharyngeus muscle. Despite the frequent absence of definite associated symptoms, it is not a normal finding and probably represents reliable evidence of neuromuscular dysfunction of deglutition. This may be an important factor in the pathogenesis of Zenker's diverticula since configurations which may represent the transition from a cricopharyngeal impression to a diverticulum have been observed.

Columbia-Presbyterian Medical Center 622 West 168th Street New York, New York 10032

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# SELECTIVE BRONCHIAL CATHETERIZATION BY A NEW PERCUTANEOUS TRANS-TRACHEAL TECHNIQUE\*

By CONSTANTIN COPE, M.D. PHILADELPHIA, PENNSYLVANIA

SELECTIVE catheterization of the major bronchi is most commonly performed by introducing a Coude or a Metras catheter through the anesthetized oropharynx or nasopharynx and glottis into the tracheobronchial tree. Such an approach has several inherent disadvantages:

- (a) toxicity from anesthetic overdosage is an ever-present danger since topical anesthesia of the pharynx and larynx must often be very meticulous;
- (b) transglottic catheterization can become a very difficult, if not impossible, task unless full patient cooperation is obtained:
- (c) laryngospasm may occur in transglottic intubation;
- (d) difficult intubations may stimulate vagal reflexes which can set off dangerous arrhythmias in patients with coexistent heart disease;
- (e) the standard sized catheters may occasionally be too large to enter a partially occluded bronchus;
- (f) since the catheter passes through nasopharyngeal secretions, it cannot be used to sample uncontaminated bronchial aspirates for culture.

For the past 3 years, the author has catheterized the tracheobronchial tree of over 100 patients for various purposes by a percutaneous transtracheal technique analogous to that which Seldinger has so successfully applied to vascular catheterization. Since the route is subglottic and the catheter consists of small diameter tubing, the method overcomes most of the objections listed above; moreover, since this technique is so easy to perform and so well tolerated by patients, it is felt that it merits a detailed description.

#### METHOD

The average adult patient is premedicated with pentobarbital 100 mg. and levopropoxyphene (Novrad) 100 mg. by mouth I hour before the procedure; 30 minutes later, codeine 60 mg. and atropine 0.4 mg. are administered subcutaneously. The patient is then placed in a supine position on a roentgenographic table which is tilted 10° head upward. The chin of the patient is raised so as to make the larynx and trachea quite prominent. The anterior aspect of the neck is prepared with an antiseptic and draped. The skin and subcutaneous tissue over the cricothyroid membrane are anesthetized with I per cent lidocaine and a nick is made with a No. 11 blade. The cricothyroid membrane or upper trachea is then pierced in the midline with a 21 gauge needle and air is aspirated to test for proper positioning, as described by Boyan and Howland. One per cent lidocaine is then injected in small volumes into the trachea. After each injection, the syringe is immediately disconnected from the needle so as to permit it to ride quite freely during coughing spells. A total volume of 2 to 6 ml. lidocaine is usually adequate to suppress cough. The needle is now exchanged for a curved 17 gauge teflon needle. It consists of a 4 inch curved 18 gauge needle with a solid bayonet point surrounded by a tightly fitting teflon envelope. The design of this needle permits it to be easily and safely threaded into the trachea by virtue of its piercing but non-cutting point and its gentle curve; once threaded, the inner needle is removed leaving the flexible plastic cannula safely in place.

<sup>\*</sup> From the Division of Radiology, Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania.

A springy tip Seldinger wire guide (external diameter 0.034 inch) is now inserted into the lower trachea through the cannula, which is then removed. A 30 cm. nonradiopaque thin wall teflon catheter with a slightly tapered tip (outside diameter 1.37 mm., inside diameter 1.07 mm.) is then threaded over the wire, advanced through the laryngeal wall and passed down to the lower level of the trachea. The Seldinger wire is pulled out and the catheter filled with contrast material, so that it may be directed under fluoroscopy into either main stem bronchus (Fig. 1). When subselective catheterization is indicated, a maneuverable metal guide is inserted within the catheter; it consists of a 35 cm. length of Seldinger wire with a sliding inner core, the distal 3 cm. of which is bent to a gentle right angle curve. A needle stop placed on the spring guide at 30 cm. from its tip indicates when the guide has reached the end of the nonradiopaque catheter. Since the inner curved spring stylet can be rotated, advanced or retracted within the ensheathing spring and catheter, a great variety of exploratory controlled motions can be made along the main stem bronchus until the opening of the segmental or subsegmental bronchus is found and intubated. A few milliliters of contrast material previously released into the main stem bronchus will make selective catheterizations quite simple. Often, entry of the catheter into the pathologic segment will be signalled by paroxysms of violent coughing which may not subside until several more milliliters of anesthetic have been instilled into this location. Following aspiration of bronchial secretions and instillation of bronchographic contrast medium, the catheter is flushed out with sterile saline and removed. If the patient is coughing at this time, finger pressure is applied over the skin puncture for 5 to 10 minutes to prevent the occurrence of subcutaneous emphysema.

## DISCUSSION

The advantage of using the Seldinger technique for tracheal catheterization can

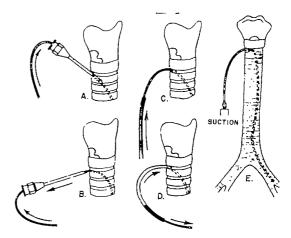


Fig. 1. Catheterization of the trachea by the percutaneous catheter-needle replacement technique of Seldinger. An intercartilaginous tracheal space or the cricothyroid membrane can be used interchangeably for puncture. Initial puncture of the trachea can be done with a styletted needle, but a teflon needle is preferred, as described in the text.

best be appreciated by pointing out that the same catheter which required a 17 or 18 gauge needle for its introduction by this technique would necessitate the use of a 14 gauge needle if the more standard "throughthe-needle" approach were utilized as described by Templeton and Fendley.

Since the cricothyroid membrane is tough and becomes more rigid and even bony with increasing age, it follows that the catheter cannot usually be of a larger external diameter than the introducing cannula. Although the author has occasionally and safely used 14 gauge needles to introduce larger radiopaque catheters into the trachea, it is felt that the larger perforation might easily lead to a greater frequency of bleeding, subcutaneous emphysema or infection. Because of these potential risks, which parenthetically have not been borne out in the literature as yet, I have been reluctant to puncture the trachea with a needle larger than 17 gauge, except under unusual circumstances.

The clear teflon catheter which is used, although small in external diameter, is, nevertheless, quite adequate to permit injection of the standard viscid broncho-



Fig. 2. Selective transtracheal bronchogram delineating a bronchial adenoma which almost completely occludes the right upper lobe bronchus. The fine catheter has bypassed the obstructing tumor, permitting the distal bronchiectatic segmental bronchi to be filled by contrast medium. This tumor was not seen during bronchoscopy.

graphic contrast media, and moreover, seems to be far less irritating than the larger stiffer radiopaque tubing. It has in fact been a source of constant surprise how well elderly patients, some with fair degrees of pulmonary insufficiency, tolerate bronchial catheterization, often with little more than a few milliliters of local anesthetic. Several elderly patients, for example, had their electrocardiograms constantly monitored by cardioscope during the stages of tracheobronchial anesthesia and selective catheterization, and no significant arrhythmias were detected at any time.

Morbidity in the early part of our experience consisted of occasional expectoration of blood-streaked sputum for about a day. However, one female patient with scleroderma lost an estimated 300 ml. of blood in about 30 minutes following such a pro-

cedure. It was thought that the 17 gauge needle which was used at that time was probably cutting through small vessels in a hypervascular cricothyroid membrane. Since redesigning the needle to include a teflon cannula and a solid bayonet trocar which has no hollow cutting point, there has been no further episode of hemoptysis.

It should also be emphasized that this needle by virtue of its flexible sheath has been extremely useful for transtracheal nonselective bronchography. It permits the patient to move quite freely without the fear that contrast medium might extravasate into the soft tissues of the neck. Occasionally, when the cricothyroid membrane is very hard, a curved 17 gauge arterial needle with a solid pointed trocar is substituted for the teflon needle.

Selective bronchial catheterization has been found to be very useful in two clinical situations. Firstly, it is valuable as a means of obtaining material for culture or tumor cell examination from an area of unresolved pneumonia. Transtracheal aspiration for bacterial or fungal sampling has been shown by Pecora<sup>3</sup> to be superior to bronchoscopic washings because it provides specimens uncontaminated by oropharyngeal secretions. The question of growth inhibition of microorganisms by local anesthetics has been brought up by Conte and Laforet.2 However, it should be noted that in their study they collected sputum together with expectorated local anesthetic, whereas in the technique used here, the aspirates are obtained in an already anesthetized field after most of the unabsorbed anesthetic has been coughed up. It is moreover unlikely that very much anesthetic can reach the pathologic segmented bronchus under study since it is partially occluded by secretions or tumor.

The second field of usefulness for the presently described technique lies in detailing partially occluding bronchial lesions. Bronchogenic carcinoma and bronchial adenoma may be difficult to delineate by gravity filling of contrast medium because

secretions accumulate proximally and distally to the lesions. In many of these cases, a fine catheter can, nevertheless, be introduced to and beyond the lesion (Fig. 2). Following aspiration of secretions for tumor cells, instillation of bronchographic medium distal to the stenosis will give a good delineation of the tumor.

Finally, it is anticipated that subselective transtracheal catheterization can play a useful therapeutic role by providing a means of instilling chemotherapeutic agents directly into a bronchus draining an abscess cavity.

#### CONCLUSION

- 1. The use of a curved teflon needle is recommended for transtracheal puncture and nonselective pronchography.
- 2. The percutaneous catheter replacement technique of Seldinger has been successfully applied to selective and subselective bronchial catheterization in over 100 patients.
- 3. It is emphasized that subselective bronchial catheterization is an important diagnostic tool that should be used not only for bronchography, but also as a means of

aspirating sterile secretions for pathologic and bacteriologic examinations.

Division of Radiology Albert Einstein Medical Center York and Tabor Roads Philadelphia, Pennsylvania

The special needles and guides mentioned in this article may be obtained from Mr. Edwin May, Assistant Director, Cardiovascular and Special Instrument Division, Becton Dickinson & Company, Rutherford, New Jersey.

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# A TECHNIQUE FOR THE SELECTIVE CATHETERIZA-TION OF SEGMENTAL BRONCHI USING ARTERIAL CATHETERS\*

By JOHN J. FENNESSY, M.B. (N.U.I.) CHICAGO, ILLINOIS

MANY different techniques for selective catheterization of segmental bronchi have been described, especially since the introduction by Metras9 of a catheter designed for this purpose. Several of the methods require the introduction of a catheter through a bronchoscope, a major disadvantage, and others require specially manufactured instruments, such as those used by Metras<sup>9</sup> and Nordenström.<sup>12</sup> Since selective bronchography is infrequently indicated, it is desirable that a technique for this purpose should be simple, convenient to use, and the instruments required should be reasonable in cost and readily available in most radiology departments. Radiopaque vascular catheters of the type described by Ödman<sup>13</sup> appear to be ideally suited for this purpose. These catheters are readily available in most radiology departments, together with the various guide wires necessary to introduce them; they have the advantage of being easily preshaped as desired, reasonable in cost and disposable. For the last several months, we have used gray Ödman arterial catheters for this purpose with very satisfactory results.

# TECHNIQUE

In the Department of Radiology of The University of Chicago, bronchographies are generally performed in the early afternoon. The patient has a full breakfast, and nothing further is taken by mouth until at least 2 hours after the examination is completed. Pre-medication is with seconal and demerol or codeine; the dose is varied from patient to patient (depending upon the patient's age and general condition); the medication is administered parenterally half an

hour prior to the examination. Anesthesia of the upper air passages is produced in the usual manner by spraying the tongue, tonsillar area, soft palate, pharynx and one nasal passage (usually the right) with a 2 per cent solution of xylocaine. Approximately 2 cc. of the anesthetic solution is then introduced into the larynx by means of a curved metal cannula, either blindly over the back of the tongue, or, preferably, directed by means of a laryngeal mirror. A soft rubber urinary tract catheter, size 12-14 French, is used for routine bronchography. The catheter is inserted through the nose and is positioned fluoroscopically in the right or left main bronchus. The catheter tip is first positioned in the potentially more abnormal side; following complete examination of this bronchial tree, the catheter is repositioned in the opposite bronchus and the procedure is repeated. The bronchial tree is outlined with contrast material by the Nordenström aspiration technique, 12 which almost invariably produces satisfactory visualization of the entire bronchial system. The catheter is left in position until the roentgenograms have been checked; when it is found that a portion of the bronchial tree is incompletely seen, a selective examination is undertaken.

A gray Ödman arterial catheter is preshaped in boiling water; the exact shape depends upon the portion of the lung to be examined. For the upper lobes, it is usually best to have a primary curve to permit easy entry and a secondary curve for placement in the desired segment or subsegment. Examples of these curvatures are illustrated in Figure 1. For the apical and apical posterior segments, a primary curvature alone is sufficient to position the

<sup>\*</sup> From the Department of Radiology, The University of Chicago, Chicago, Illinois.

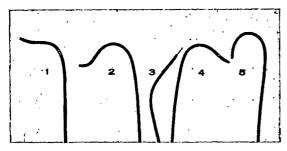


Fig. 1. Catheter shapes. (1) For the lingula of the left upper lobe. (2) The anterior segment of the left upper lobe or the posterior segment of the right upper lobe. (3) A slightly curved catheter for the basal segments of both lower lobes. The flexible end of a guide wire is protruding from the tip of the catheter. (4) For the anterior segment of the right upper lobe or the posterior division of the apical-posterior segment of the left upper lobe. (5) For the apical segments of the upper lobes. For the middle lobe and superior segments of the lower lobes, the tip of the catheter is curved approximately 90° or slightly less.

catheter; however, for anterior, lingular and posterior segments, a short secondary curve may be added about I cm. from the tip. The catheters are shaped in the same configuration as the instruments described by Metras. For the middle and lower lobes, a single curve is sufficient for placement in the orifice of the bronchi and a secondary curve is added if it is necessary to enter a secondary segmental division. We generally keep a supply of pre-shaped catheters on hand to avoid delay. However, even if none is available, they can be quickly prepared.

A No. 160 vascular guide wire is passed, flexible end first, through the rubber catheter, which is then removed over the guide wire, leaving the wire in position in the bronchial tree. The arterial catheter is then introduced into the bronchial tree over the guide wire. A No. 160 guide wire is used, since this passes easily through the side hole at the end of the rubber catheter, whereas the larger No. 205 wire does not. Once the tip of the catheter has been placed in the bronchial tree, it can be manipulated very simply into the desired lobar segment under fluoroscopic control. The curvature at the tip of the catheter is controlled by

the guide wire. The farther the wire is advanced into the catheter, the straighter the tip becomes; by altering the curvatures, it is possible to enter the desired region of the bronchial tree very easily. After the catheter has been positioned in the desired pulmonary segment, it may be either advanced peripherally and contrast material injected during withdrawal, or the contrast material may be injected at the orifice of the bronchus. If the area is atelectatic, it is better to advance peripherally and inject during withdrawal, injecting alternately small amounts of contrast medium and air to produce an even filling of the region with an air contrast examination of the bronchial walls. Care must be taken to inject slowly and the injection should be monitored fluroscopically to avoid over-filling of the alveoli. If, after the first cubic centimeter of contrast has been injected, evidence of bronchiectasis is seen, aspiration may be performed to permit better definition of the cavities. Obstructing lesions may be bypassed if the stenosis is not complete by first passing the flexible end of the guide wire distal to the obstructing lesion and then threading the catheter over the guide wire.

If the preliminary examination of the chest reveals an area of atelectasis or other abnormality in the lung, it is usually desirable to perform the entire examination with the Ödman catheter, which has been preshaped in anticipation of performing a selective injection. The catheter is preshaped, depending upon the portion of the pulmonary tree to be entered, and a No. 205 vascular guide wire is placed within it, stiff end first, to straighten the curves. After lubrication with viscous xylocaine, it is passed into the anesthetized nostril and advanced gently until the tip comes in contact with the posterior wall of the nasopharynx. At this point, the guide wire is retracted 2 to 3 cm., permitting the tip of the catheter to curve downward toward the larynx. Under fluroscopic control, catheter and guide wire are directed downward until the tip lies just above the glottis. The

patient's head is then positioned as for indirect laryngoscopy with the chin tilted slightly forward and the tongue protruding. The guide wire is again advanced to within a centimeter or so of the tip of the catheter and, during abduction of the cords by deep inspiration, the catheter is gently passed into the trachea. If the tip of the guide wire is kept about a centimeter proximal to the tip of the catheter, the latter assumes a slight curve, enabling it to glide easily down the trachea without catching on any of the tracheal rings. It is usually desirable to withdraw the guide wire and to inject I to 2 cc. of I per cent xylocaine just above the carina before advancing into the selected main bronchus. The guide wire is then repositioned and the catheter is placed in the main bronchus and advanced just distal to the expected point of origin of the segmental or lobar bronchus to be catheterized. Routine bronchography may now be performed in the usual manner, or the abnormal segment may be selectively injected. When a selective injection is decided upon, the guide wire is partly withdrawn from the catheter, permitting the tip to curve, and the catheter is then either withdrawn or advanced until the tip falls into the desired bronchial orifice. Blind catheterization of lobar segmental bronchi is easily performed, using the carina as a point of reference. One can expect the orifice of the right upper lobe bronchus to arise I to 2 cm. distal to this point in the majority of patients, and the left upper lobe bronchus 4 to 5 cm. distal. The upper lobe bronchi pass almost directly laterally and accordingly the patient should be positioned facing the fluroscopic image intensifier to enable one to control entry of the catheter into these regions. For catheterization of the middle and lower lobe bronchi, the patient is placed in a lateral position and the catheter is manipulated with the tip pointing anteriorly or posteriorly, depending on whether one intends to enter ventral or dorsal segments. The posterior basal segment is the simplest region to enter, since any object introduced into the

bronchial tree will almost automatically fall into that region. To enter the lateral basal segment, it is usually simplest to first advance the catheter into the posterior basal segment, then withdraw slightly with the tip of the catheter curved so that it is pointing laterally. The most difficult segment to catheterize is the medial basal segment, since this bronchus is frequently small if present.

#### RESULTS

This report concerns the use of this method of selective catheterization of segmental bronchi which has been attempted on 39 patients. All pulmonary segments have been catheterized at least once.

We are unable to enter the desired segment in 8 of these patients. In 3 patients the bronchus was totally obstructed by a tumor; in 3 others the wrong segment was catheterized in patients who did not have a previous bronchogram, and in 1 patient insufficient local anesthetic was used and the catheter was displaced from the segmental bronchus by coughing. One patient was uncooperative and the examination had to be discontinued before the correct region was catheterized.

The procedure is no more uncomfortable for the patient than a routine bronchography and has frequently yielded useful additional information. Provided adequate anesthesia of the tracheobronchial tree has been attained, the only discomfort noted by the patients has been a sensation of pressure in the nasopharynx and nose while the guide wire is in position within the catheter. The youngest patient on whom the procedure was performed was a 14 year old boy with a pneumonia-like lesion in the anterior segment of the right upper lobe, which proved to be a metastatic sarcoma. The oldest patient was a 73 year old male with a postinflammatory stricture of the apical posterior segment of the left upper lobe.

One patient developed a segmental pneumonia following the examination. In this patient, the posterior division of the apical posterior branch of the left upper lobe bron-

chus was selectively catheterized and the area was inadvertently over-filled with contrast material, which rapidly alveolarized and remained in the alveoli for over a week. The area had been irrigated with Ringer's solution prior to the injection of contrast material in an attempt to obtain a cytologic specimen from a peripheral mass; it has been our experience that alveolarization of contrast medium is much more likely to occur under these circumstances.

#### DISCUSSION

A selective injection of contrast material is indicated whenever routine bronchography fails to completely fill a portion of the bronchial tree. 6,7 Nonvisualization or inadequate filling of a portion of the lung may be a result of either a mechanical obstruction of the supplying bronchus or of disease of the lung parenchyma interfering with the normal respiratory suction mechanism. It is especially important to fully demonstrate the bronchial anatomy in atelectatic segments in order to exclude an occult neoplasm as the cause of the collapse. If it can be demonstrated that the bronchus supplying an atelectatic lobe or segment is normal, neoplasia is almost certainly excluded.2 A smoothly tapering stenosis with bronchiectatic changes periphally is most likely inflammatory in origin<sup>6</sup> (Fig. 2), whereas an irregularly stenotic lesion with indentation and narrowing of the adjacent bronchi and failure of filling of the smaller side branches is almost certainly malignant<sup>10</sup> (Fig. 3, A and B). Occasionally, a bronchus may be occluded by secretions or blood clots; these may be removed by selective catheterization and irrigation of the region prior to the injection of contrast material (Fig. 4, A and B; and 5). Filling of the upper lobe bronchi in patients with old tuberculous processes is often only partially successful,5 and a complete examination will require selective injection of the region. A directed injection of contrast material may also be indicated in some patients with a markedly reduced respiratory reserve (as a result of emphysema or other

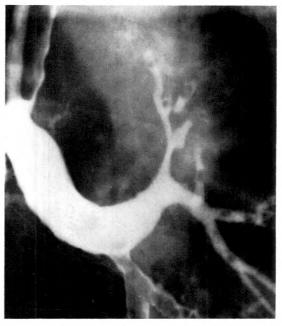


Fig. 2. A routine chest roentgenogram demonstrated a mass in the left upper lobe of this asymptomatic 73 year old male. The apical-posterior bronchus of the left upper lobe was selectively catheterized and injection of contrast material revealed a smoothly tapering stenosis with bronchiectatic changes peripherally. The appearance was considered consistent with a postinflammatory stricture. Repeated sputum examinations revealed no tubercle bacilli or abnormal cells. Washings obtained from the segmental bronchus prior to the injection of contrast material also revealed no abnormality. The lesion has not altered in the last year and the patient remains asymptomatic.

generalized pulmonary disease) in whom a localized lesion has been seen on chest roentgenograms, since even a unilateral bronchography is contraindicated if the maximum breathing capacity is less than 35 per cent of normal. 11 Controlled injection of medication into lobar segmental divisions of the bronchial tree has been frequently described. Recently, Saeed<sup>15</sup> has described a method for the treatment of tuberculosis, using medication injected through Metras catheters, and Ramirez-R.14 has described a technique for the treatment of pulmonary aspergilloma by intrabronchial infusions of amphotericin B and sodium iodide. In recent years, exfoliative cytology has assumed an increasing role in

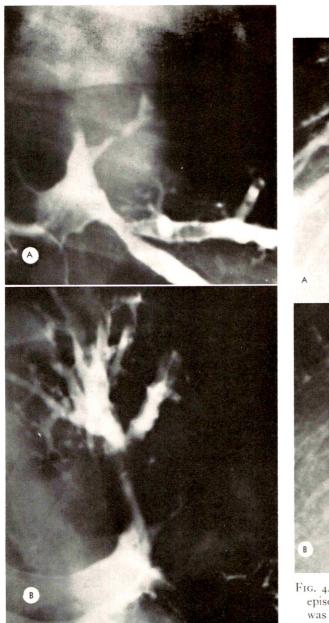


Fig. 3. Neoplastic stricture of the apical-posterior segmental bronchus of the left upper lobe with involvement of the anterior segmental bronchus and the origin of the lingula. (A) A routine bronchogram shows nonfilling of the apical-posterior segment. (B) The segmental bronchus was selectively catheterized. The catheter has passed the stenosis, revealing crowding of the peripheral bronchi as a result of atelectasis, without evidence of bronchiectasis.

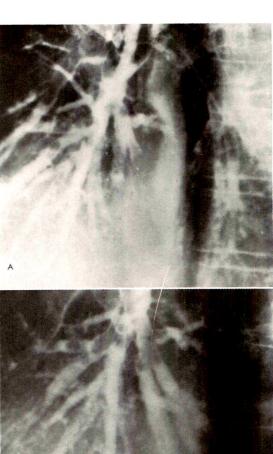


Fig. 4. This 50 year old female experienced several episodes of hemoptysis. At bronchoscopy blood was seen coming from the posterior basal bronchus on the left. (A) A routine bronchogram showed obstruction of the posterior and lateral basal segmental bronchi near their origin. (B) The obstructed segments were selectively catheterized, clotted blood was aspirated following irrigation with Ringer's solution, and the bronchi were then filled to the periphery with contrast material. There is no obstruction; bronchiectatic changes are seen.

the diagnosis of bronchogenic carcinoma, and attempts have been made to obtain specimens from lung lesions beyond the reach of the bronchoscopist by Friedel,<sup>3</sup> Hattori *et al.*<sup>4</sup> and others. We have been investigating this further possible application of selective bronchial catheterization with so-far inconclusive results and are presently attempting to obtain cytologic specimens from peripheral lung lesions by

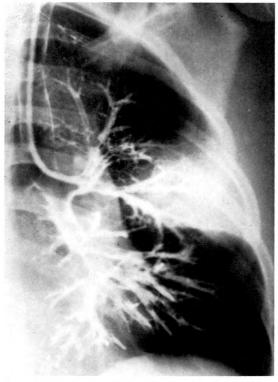


Fig. 5. This 14 year old boy presented with a history of severe hemoptysis of 2 weeks' duration. A chest roentgenogram revealed consolication of the anterior segment of the right upper lobe. A vascular sarcoma had been resected from the left scapular area I year previously. At bronchoscopy, bleeding from the orifice of the left upper lobe bronchus was noted. The segment was selectively catheterized. the area was irrigated with Ringer's solution, and the aspirate retained for cytologic and bacteriologic examination. Examination of the aspirate revealed only red blood cells. Following irrigation, selective and routine bronchography was performed, using the same catheter. Patent segmental bronchi were demonstrated, At thoracotomy, the surface of the lung was studded with small, hemorrhagic, tumor nodules; there was extensive hemorrhage into the parenchyma of the anterior segment.

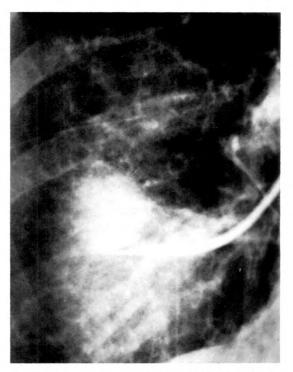


Fig. 6. A chest roentgenogram revealed a mass in the right lower lobe of this 60 year old female. Bronchoscopy and sputum cytology revealed no abnormalities. The segment containing the lesion was catheterized and the tip of the catheter was placed as close as possible to the lesion. A small brush was then passed through the catheter and advanced to the mass; slides were prepared directly from the brush. Cells "exhibiting findings suspicious for malignancy" were present. At thoracotomy, a squamous cell carcinoma was removed.

means of irrigation of the involved segments or by passing small brushes and other instruments peripherally through the catheter under fluoroscopic control (Fig. 6). Perhaps the most widely used instruments for selective catheterization of lobar and segmental bronchi are the pre-shaped catheters described by Metras.9 These are relatively radiopaque, stiff rubber catheters with a slightly conical tip to permit easy introduction into the segments; they are manufactured in various shapes designed for the examination of specific areas of the lung. Nordenström<sup>12</sup> has described a catheter which is pre-shapable and disposable and also has the advantage of being radiopaque. It is approximately the same

size as the Metras catheter with an external diameter of about 5 mm. and, like the Metras catheter, is designed to be introduced through the mouth over a special metal mandrin. Maassen<sup>8</sup> uses a catheter with two inflatable cuffs separated by a short interval with the opening between the two cuffs. One cuff is placed above the segment to be filled, the other below it, and the region between is flooded by the pressure of injection. More recently, Virtama<sup>17</sup> has described a method for the introduction of Ödman catheters into the bronchial tree, using a specially constructed Perspex spatula to guide the catheter and guide wire over the tongue and into the trachea. Steckel and Grillo<sup>16</sup> have introduced arterial catheters into the trachea percutanes ously by the Seldinger technique. Segmental catheterization during bronchoscopy has also received considerable attention and has been described in detail by Kassay et al. and others. Selective catheterization of various bronchi by the Metras and Nordenström catheters is easily performed; however, their relatively large size, compared with the arterial catheters, is a disadvantage, as is the fact that they must be introduced through the mouth. It has been our experience that it is easier to introduce a catheter into the trachea through the nasal cavity than through the mouth; manipulation is also easier for the operator and more comfortable for the patient by this approach. Also, catheters may be dislodged from the orifice of segmental bronchi by movements of the tongue and lips. The obvious disadvantage of Maassen's catheter is that the segmental bronchi generally arise opposite or adjacent to one another as, for example, the middle lobe and apical segment of the lower lobe, and the pressure required to fill an atelectatic or otherwise abnormal segment would be more than sufficient to flood the adjacent normal segment with the risk of producing a localized pneumonia. Selective catheterization during a bronchoscopic examination has been described by Kassay et al., Chase and others. Kassay uses spe-

cially manufactured rubber catheters while Chase guides a urinary tract catheter into the desired area by means of a special attachment to the bronchoscope. The percutaneous approach described by Steckel and Grillo is reported by them to be easily performed with very little discomfort to the patient. However, it seems to us that it is inadvisable to produce an artificial communication between the skin and trachea when there is available a normal and easily accessible channel suitable for the same purpose. While it is admitted that the risks of percutaneous catheterization may be slight in experienced hands, they are real and have been reported by Zucherman and Jacobson<sup>18</sup> and others. Virtama's use of an Ödman catheter passed through the mouth requires a specially manufactured Perspex spatula, and again, as in all orally placed catheters, there is the disadvantage of displacement of the tip by movements of the tongue or lips.

## SUMMARY

A technique for the selective catheterization of segmental and subsegmental bronchi by means of radiopaque vascular catheters has been described. The indications for the procedure have been discussed and a possible application of this method to the diagnosis of bronchogenic carcinoma and other pulmonary neoplasms has been mentioned.

Department of Radiology The University of Chicago 950 East 59th Street Chicago, Illinois 60637

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#### VIDEO TAPE RECORDING OF TRACHEO-BRONCHIAL DYNAMICS\*

By FRED J. HODGES, M.D., WALTER M. WHITEHOUSE, M.D., ARTHUR C. KITTLESON, M.D., and LAWRENCE R. GRIEWSKI, M.S.E.E.

ANN ARBOR, MICHIGAN

THE observation of tracheobronchial movements is but one of many useful applications of video tape recording in clinical radiology. Only a few years ago, the necessary instruments were extremely complicated, costly and of limited availability. Costs are dropping and a number of dependable, fully transistorized portable television tape recorders of domestic and foreign manufacture are being marketed. As initial technical and financial restrictions become less and less imposing, the time has come to consider the practical worth of this new method of information storage. If found to be valuable, it may gain wide practical application. Presently, there are two techniques available for recording roentgenologically demonstrable motion—cinefluorography and video taping. If the latter system lacks true practicability on any score, if it does not add materially to excellence and versatility of roentgenologic diagnosis, it should not and will not long survive.

PRINCIPLES AND INSTRUMENTATION
OF TELEVISION MONITORING AND
RECORDING OF FLUOROSCOPY

The television camera, which is the source of information for the video tape recorder, incorporates electron beam scanning as a fundamental device. The image observed on the television monitor is the reassembly of accurately timed sequential bits of information from the television camera (or video tape recorder) which are read out by an electron beam within the picture tube upon its phosphorescent material-coated interior face with tremendous speed and remarkable accuracy. The observer is there-

by presented with a mosaic picture rather than one with continuous light values.

In roentgenologic procedures, the television camera may read fixed or changing images: (1) directly from a conventional fluoroscopic screen, (2) with the aid of optical size reduction, (3) from the output screen or phosphor of an electronic light amplifier, and (4) from the output phosphor of a fluoroscopic image intensifier tube. We have chosen the last named system. Two major types of television camera are in common use. Vidicon cameras are compact, light weight and relatively inexpensive. Orthicon cameras are bulkier, heavier and considerably more expensive. Although vidicon cameras of improved design and performance are appearing on the market, certain inherent characteristics are to be expected. These cameras operate best at relatively high light levels, which means high input roentgen-ray level. In vidicon tubes "stickiness" or image persistence introduces blurring when movement is being observed. Orthicon cameras, on the other hand, are most efficient at low light levels, requiring low roentgen-ray input, and there is virtually no image persistence. In our experience, the added cost and bulk of orthicon cameras are amply outweighed by improved performance. Once the fluoroscopic image has been translated into television language, it can be transmitted by closed circuit to a remote recorder or fed into a portable recorder in the fluoroscopic room.

PRINCIPLES AND INSTRUMENTATION
OF CINEFLUOROGRAPHY

Fluoroscopic findings can be recorded by

From the Department of Radiology, The University of Michigan, Ann Arbor, Michigan.

<sup>\*</sup> Presented at the Sixty-fifth Annual Meeting of the American Roentgen Ray Society, Minneapolis, Minnesota, September 29-October 2, 1964.

moving picture camera equipment in a variety of ways: (1) direct filming of a conventional fluoroscopic screen using refractor or mirror optical systems, (2) from the output phosphor of an electronic light amplifier tube, (3) from the output phosphor of a fluoroscopic image intensifier. Any of the above systems can be combined with synchronizing devices to suppress roentgen-ray production during film transport. Variable speed of recording is possible.

Cinefluorography can be controlled by direct mirror viewing of the image or by television monitoring if a beam splitter is used to divert a part of the light from the cine-camera. Once exposed, well controlled photo processing and projection are required for viewing of cine-film results.

### RELATIVE COSTS OF VIDEO TAPING AND CINEFLUOROGRAPHY

Each of the recording systems depends upon basic roentgenologic apparatus. Beyond this, the instruments needed for video tape recording and cinefluorography do not differ sufficiently in over-all cost to create an important price differential. There are deluxe and austerity models of each to be had.

# RELATIVE ADVANTAGES OF VIDEO TAPING AND CINEFLUOROGRAPHY IN VARIOUS ROENTGENOLOGIC ADAPTATIONS

These two systems should not be considered competitive because each excels in some particulars. The major advantages of cinefluorography are: (1) high image resolution, and (2) wide range of recording speed. Its disadvantages are: (1) higher input radiation requirement, (2) time delay between recording, viewing and broadcasting and (3) fallibility of processing techniques.

The major advantages of video tape recording are: (1) immediate visual control of recording quality, (2) elimination of photo processing, (3) no increase in radiation input over fluoroscopic level, (4) possibility of

simultaneous closed circuit broadcasting for teaching purposes, and (5) immediate repeated play back to permit re-recording when necessary or desirable. Its disadvantages are: (1) mosaic image contains less information than cine-film, (2) editing of tape is more difficult than in the case of film, (3) television camera and tape recorder introduce additional electronic circuitry and servicing requirements, and (4) "slow motion" filming is impossible.

When the ultimate in image resolution is not essential to valid roentgenologic interpretation, video tape recording is extremely useful and highly practicable. The cinefilm used to illustrate video taping in bronchography required transfer from the original to a second tape in the editing of various sequences. Every transfer of recorded signals results inevitably in resolution losses. Once edited the resulting tape is further degraded by subjection to kinescopic filming and processing. It is hoped that, thus projected for a large audience, it will be found that the amount of information captured and retained by the television tape recording method will be adequate to provide a meaningful demonstration of tracheobronchial dynamics.

#### TRACHEOBRONCHIAL DYNAMICS

Tracheobronchial dynamics as demonstrated by video tape recording may be divided into three general groups: (1) apnea and quiet respiration, (2) deep respiration, and (3) coughing.

(1) Apnea and quiet respiration are characterized in the segmental and subsegmental bronchi by transmitted heart motion. Minimal bronchial rotation and rise and fall are seen with quiet diaphragm motion. There is very minimal inspiratory dilatation and expiratory narrowing of the trachea and major bronchi. We are unable to detect bronchial peristalsis. For bronchial evaluation, the decubitus position with a horizontal beam and complete bronchial fill are used. Apnea for short periods is obtained by patient cooperation and the position, due to pressure from abdominal

organs, reduces diaphragm excursion in quiet respiration.

- (2) In deep respiration, transmitted heart motion is less obvious. With the expiratory rise and inspiratory fall of the bronchi and trachea, a shortening and lengthening are found. The rotational element is more noticeable and the inspiratory dilatation and expiratory narrowing are more marked. Bronchial and tracheal expiratory narrowing and shortening may have been the source of previously reported bronchial peristalsis. In one emphysematous patient no specific bronchial narrowing or abnormality was visualized, but a prolonged expiratory phase was evident.
- (3) Cough is a striking phenomenon. The glottis is opened for a brief inspiratory effort (alveolization of contrast occurs) and then the glottis closes firmly. The appearance remains static briefly while intrathoracic pressure increases. With opening of the glottis, the intrathoracic trachea and the major bronchi are abruptly narrowed.\* The shortening, rotation and rise of the bronchi are all exaggerated. In tracheobronchiomegaly (Mounier-Kuhn syndrome), these phenomena are present and tracheal and bronchial diameter changes are particularly striking. When coughing
- \* From an associated study, we have found that 60 per cent of unselected patients show 50 per cent or more tracheal collapse with cough. Children of 5 and under with no history of lung infection show no collapse. In a group of smokers and nonsmokers with no history of lung infection, the smokers are easily recognized because of consistently more marked tracheal collapse.<sup>2</sup>

occurs, tracheal and bronchial collapse is virtually complete.<sup>1,3</sup>

#### SUMMARY

- 1. Our impressions of orthicon and vidicon television systems coupled with tape recording are compared with cinefluorographic methods. We have chosed orthicon television with a transistorized portable tape recorder as the best system for general departmental use.
- 2. Normal bronchial dynamics as demonstrated with the above system are presented in apnea and quiet respiration, deep respiration and coughing. Preliminary observation of dynamic abnormalities is mentioned.

Fred J. Hodges, M.D.
Department of Radiology
The University of Michigan
Medical Center
Ann Arbor, Michigan 48104

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#### ROENTGENOGRAPHIC FEATURES OF MUCOID IMPACTION OF THE BRONCHI

By VICTOR CARLSON, M.D.,\* JOHN E. MARTIN, M.D.,\* J. M. KEEGAN, M.D.,\* and J. E. DAILEY, M.D.† HOUSTON, TEXAS

IN 1951, Shaw³ discussed a distinct clinical entity which had not been previously reported in the medical literature, and to which he gave the descriptive term "mucoid impaction of the bronchi." He reviewed the clinical, roentgenographic, and pathologic findings in 10 patients, all of whom had a history of bronchial asthma or chronic obstructive bronchitis.

It was not until 1957 that articles concerning mucoid impaction of the bronchi again appeared in the literature. At this time, Shaw, Paulson, and Kee<sup>4</sup> published a study of 36 additional patients, each of whom gave a history of bronchial asthma, hay fever, or chronic obstructive bronchitis. That same year Greer1 published a study of 8 new cases and Harvey, Blacket, and Read2 reported 9 other cases. These authors further described the clinical findings as well as the pathologic and roentgenographic findings.

In 1963, Sheehan and Schonfeld<sup>5</sup> illustrated the difficulty in differentiating mucoid impaction of the bronchi roentgenographically from bronchogenic carcinoma. In 1964, Wilson<sup>6</sup> published a study of 3 cases of mucoid impaction of the bronchi.

In reviewing the reported articles, it becomes apparent that the roentgenographic features of mucoid impaction of the bronchi might simulate those of other pulmonary diseases, notably, malignant neoplasm, tuberculosis, pulmonary abscess or chronic suppurative pneumonitis. The difference in management and the great variance in prognoses of these pulmonary diseases make the recognition of mucoid impaction of the bronchi important. The purpose of the authors is to evaluate the roent-

genographic criteria of 6 proved cases of mucoid impaction of the bronchi.

#### CLINICAL COURSE

The clinical course in almost all of the patients described in the literature is one of a long history of allergic asthma, hav fever, or chronic obstructive bronchitis with the attendant sequelae to these diseases, i.e., lassitude, prolonged low grade fever, weight loss, anorexia, chronic productive or nonproductive cough, and in some instances, hemoptysis. Only 1 of 6 patients in our series had a history of recent bronchial asthma. Probably one of the most important diagnostic clinical findings in these patients is that of the expectoration, on many occasions, of hard, rubbery mucoid plugs. Following the expectoration of the plugs, there may be expectoration of purulent material after which there is improvement of clinical symptoms.

Many of the chest lesions described in the literature were discovered on routine chest examinations rather than being related to acute disease. This was also true in all of the cases in our group. Although most had a history of chronic cough, none were acutely ill at the time of their original chest roentgenogram. There is no apparent age or sex distribution of this disease. At least one third of all of the patients, including ours, had a history of hemoptysis.

#### PATHOLOGY

A marked similarity in both the gross and the microscopic pathology is noted throughout the reported cases. These impactions are located within markedly dilated bronchi. They present as a greenish-gray or

<sup>\*</sup> Department of Radiology, St. Joseph's Hospital, Houston, Texas.

brownish-gray viscid thick material, sometimes attaining a size as large as 2.0 to 3.5 cm. in length and 1.0 to 2.5 cm. in width. They are most frequently found in segmental or second order bronchi, just distal to a bifurcation. A mucus plug is apparently developed by a progressive layering of inspissated mucus within the bronchus until the lumen is completely occluded. As the mucus collects, the dilated bronchus may compress neighboring bronchi to initiate formation of further impactions.

Figure 1A demonstrates the appearance of an operative specimen showing the grayish, inspissated mucus plug within the bronchial lumen. Figure 1B demonstrates the mucus plug after its removal from the bronchial lumen.

The bronchi are markedly dilated and there are changes in the normal ciliated columnar epithelium, which may be replaced by squamous epithelium or may be completely destroyed. The cartilaginous elements may also be destroyed. The most consistent feature of the gross pathology is the hard, inspissated material within the dilated bronchus.

From a microscopic standpoint, infiltration of the bronchial wall by lymphocytes and eosinophils is rather characteristic of this entity. Adjacent alveoli may remain intact but may be filled with amorphous pink staining material laden with eosinophils, plasma cells, leukocytes, lipophages, and occasional foreign body giant cells. These microscopic findings may have led pathologists to label this as "eosinophilic granuloma" or "lipoid granuloma" before mucoid impaction of the bronchi was recognized as a distinct clinical entity.

#### ROENTGENOGRAPHIC FEATURES

To date, a total of 67 cases of mucoid impaction of the bronchi have been reported. Our 6 new cases are reported with special emphasis on the roentgenographic features which we believe are sufficiently characteristic to suggest the diagnosis.

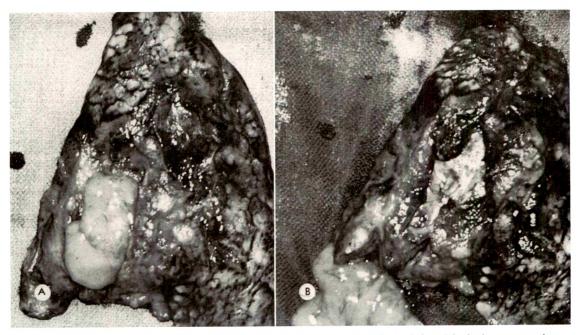


Fig. 1. (A) Surgical specimen of a mucoid impaction in situ in the right lower lobe with the lung parenchyma separated and the bronchial lumen opened. Note the thick tenacious character of the mucoid impaction. (B) Same operative specimen as seen in A. The mucoid impaction has been lifted from its bed in toto with a pair of forceps.

Some of these features have been noted by other authors and some have not had previous recognition. These are as follows:

I. The lesions may be elliptical, rounded or oval. They are usually smoothly marginated owing to the fact that the shadows cast are those of dilated bronchi filled with inspissated mucus (Fig. 2). If numerous adjacent bronchi are involved in one segment of the lung or in adjacent segments or subsegments of lung, the roentgenographic picture of the lesion may present a "cluster-of-grapes" appearance (Fig. 3).

II. The lesions are frequently "V-shaped" with the apex of the "V" towards the hilus (Fig. 4, A and B). This configuration is easily understood since the impactions often occur in second order bronchi, just distal to and often involving a bifurcation.

III. The lesion is rarely, if ever, clearly visualized on both the posteroanterior and the lateral chest roentgenograms owing to the branched linear configuration of the bronchial tree. That projection in which the long axis of the lesion is at right angles to the viewer demonstrates the lesion most

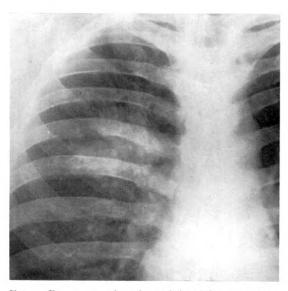


Fig. 2. Posteroanterior view of the right upper lobe showing rounded and oval densities that are relatively smoothly marginated, converging upon the right hilus.

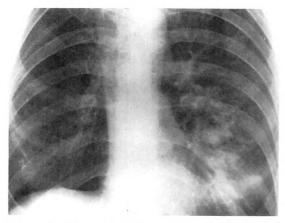


Fig. 3. Posteroanterior view of the chest revealing numerous rounded oval densities in the lower lobe and involvement of the numerous adjacent bronchi by impacted mucus, giving a "cluster-of-grapes" appearance.

clearly. Figure 5, A and B shows the posteroanterior and lateral views of the same chest demonstrating the lesion in the right lower lobe. On the lateral roentgenogram (Fig. 5B), it can be seen that the lesions have the characteristic rounded and oval configurations, whereas on the posteroanterior roentgenogram (Fig. 5A), the lesion is portrayed as an infiltrative process only, the nature of which is unclear in this single projection.

IV. If portions of the dilated bronchi are filled with mucus plugs and other portions are unfilled, air bronchograms may be noted in the unfilled dilated segments.

V. The lesions are most frequently found in the upper lobes but they may occur in any lobe. It is not unusual to find an early developing mucoid impaction in a quadrant of a diseased chest, while in another quadrant there is an area of resolving mucoid impaction. Figure 6 shows the presence of a mucoid impaction in the left upper lobe of one of our cases. Figure 7 is another posteroanterior study of the same chest made 5 years later in which the mucoid impaction in the left upper lobe has resolved but in which there is now diffuse involvement of the left lower lobe. Frequently, many areas of involvement may be visible at the same

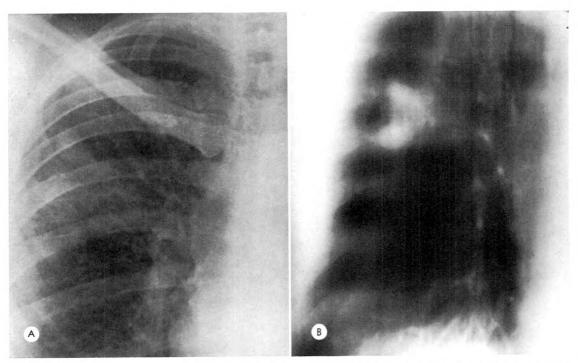


Fig. 4. (A) Posteroanterior roentgenogram and laminagram of the right upper lobe demonstrating mucoid impactions involving the bronchi to the anterior and posterior segments of the right upper lobe. Impacted mucus in these bronchi forms a characteristic "V" configuration as the bronchi converge upon the right upper lobe bronchus.

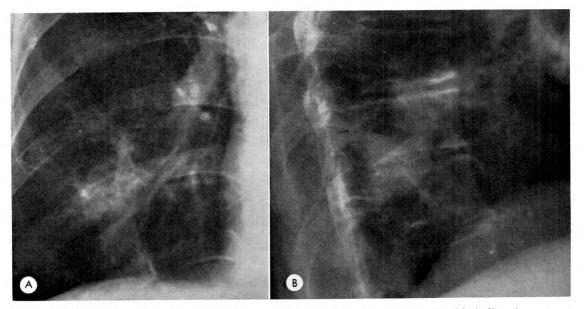


Fig. 5. (A) Posteroanterior roentgenogram of the right upper lobe showing a nonspecific infiltrative process without clear definition. (B) Lateral roentgenogram of the same lesion demonstrating the characteristic rounded and oval configuration of the mucoid impaction.

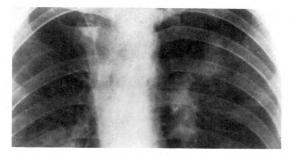


Fig. 6. A typical lesion in the left upper lobe with a rounded and oval configuration. This lesion responded to medical treatment satisfactorily: however, note the surgical changes in the right upper lobe, secondary to previous segmental resection for a mucoid impaction.

time in different stages of development. The reason for the distribution of these lesions is not clear at this time. It has been suggested that the development of the lesion is in some way related to the production of a thicker, more tenacious bronchial mucus secretion in those individuals with bronchial asthma or chronic pulmonary disease.

VI. The roentgenographic picture is trequently a combination of findings; those described above, as well as associated segmental atelectasis and pneumonic infiltration or cystic bronchiectasis distal to the bronchial occlusion (Fig. 8).

It has been noted by previous authors and in several of our cases that the development of a mucoid plug may be identified in an area previously not involved, only to be followed by the disappearance of the same lesion on follow-up roentgenograms, after medical management of the patient and without benefit of surgery.

#### DIFFERENTIAL DIAGNOSIS

Mucoid impaction of the bronchi may simulate many diseases of the lung, espe-

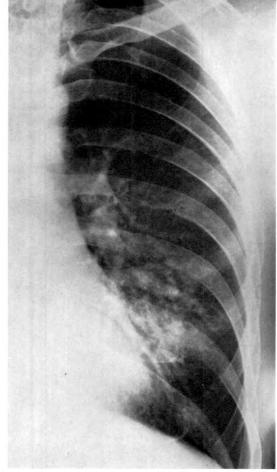


Fig. 7. Same patient as shown in Figure 6. This posteroanterior roentgenogram, made 5 years later, shows that the lesion in the left upper lobe has cleared satisfactorily, but that now there is diffuse involvement of the left lower lobe.

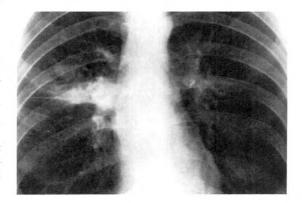


Fig. 8. Posteroanterior roentgenogram of the chest showing segmental atelectasis and pneumonic infiltration superimposed on an area of mucoid impaction.

cially malignant neoplasm, tuberculosis, pulmonary abscess, or chronic suppurative pneumonitis. However, a history of allergic type disease with an associated history of a hard or rubbery type sputum would suggest a diagnosis of a possible mucoid impaction, especially if concurrent typical roent-genographic findings are present. In some cases, a differentiation between mucoid impaction of the bronchi and malignant neoplasm is impossible prior to thoracotomy.

#### SUMMARY

Previous articles on mucoid impaction of the bronchi have been reviewed and 6 new cases are reported, with special regard to the roentgenographic characteristics of this entity. Although only recently described, this entity has a somewhat characteristic appearance on the chest roentgenogram which might allow a specific roentgenographic diagnosis. The criteria for roentgenographic diagnosis are enumerated and the differential diagnosis is considered.

Victor Carlson, M.D.
Department of Radiology
St. Joseph's Hospital
1919 La Branch
Houston, Texas 77002

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#### MUCOID IMPACTION OF THE BRONCHI\*

By S. H. TSAI, M.D., and JOHN W. JENNE, M.D. MINNEAPOLIS, MINNESOTA

THE syndrome of mucoid impaction of the bronchi was first described by Shaw, who in 1951 and 1957 reported a total of 41 cases. <sup>12,18</sup> An additional 50 cases were recorded in the English language literature. <sup>2,8,6,8,14–17</sup> Several reports have also appeared in continental Europe. <sup>16</sup> The great majority of all these patients had a history of asthma.

#### PATHOLOGY

The tenacious mucoid sputum of some asthmatic subjects tends to be retained and inspissated within a bronchus, often a segmental or subsegmental branch. If this is not dislodged, further layers of dried mucus may be deposited, resulting in impaction. The growth of the impaction is both longitudinal and circumferential. Circumferential enlargement distends the bronchus. The bronchial wall is eventually damaged by the pressure and the associated infection unless the impaction is coughed up in the early stages. Obstructive pneumonitis with or without segmental collapse develops distally and, if the impaction persists, becomes irreversible. Cystic bronchiectasis, lung abscesses, and fibrosis are then the inevitable sequelae.6,12

The impaction is in the form of a tubular cast or plug which may be branched. It has a greenish gray color and a putty-like consistency. Its cut surface frequently appears laminated. Specimens up to 6.6 cm. in length and 2.5 cm. in diameter have been described. Microscopically, it consists of homogeneous eosinophilic material and nuclear debris.<sup>6,12</sup>

#### ROENTGEN FINDINGS

The impaction, when of sufficient size and density, may be visible on routine roentgenograms and laminagrams of the chest. Its appearance is characteristic. When seen in profile, it presents itself as an elongated opacity with undulating borders (Fig. 1, A and B; 2; and 7A). Often one observes a pair of impactions forming a V with the point toward the hilus (Fig. 1B; 2; and 7A). They may simulate a cluster of grapes (Fig. 7A). When the impaction is seen on end, it appears as a well-defined, round opacity (Fig. 5A; and 6A). When the cross section of an impaction is shown on a laminagram, it is very sharply demarcated, uniformly dense, and round, oval, or elliptic in shape (Fig. 6B).

A clear air space is often left behind after a bronchus is emptied of the impaction (Fig. 5B). A radiolucent defect within the opaque shadow of an impaction indicates that a fragment of it has been dislodged (Fig. 7B).

The roentgen picture of segmental collapse, obstructive pneumonitis, and abscesses secondary to the impaction needs no particular comment. The multiple, large bronchiectatic cavities filled with thick exudate, however, may occasionally present an image similar to that of a lobulated tumor.<sup>14</sup>

The bronchographic feature is occlusion of the affected bronchus (Fig. 2; and 4, A, B and C). Filling defects caused by mucus may be present near the site of occlusion (Fig. 4, B and C). A typical picture is produced when the opaque impaction or cast is seen beyond the point of obstruction (Fig. 2; and 4, A, B, and C)

The impaction may be located in one or more lobes. There is a definite preponderance of upper lobe involvement. A less effective tussive mechanism in this portion of the lung has been postulated as a possible explanation.<sup>18</sup>

Mucoid impaction is easily mistaken for

<sup>\*</sup> From the Departments of Radiology and Medicine, University of Minnesota Medical School and Minneapolis Veterane Hospital, Minneapolis, Minnesota.

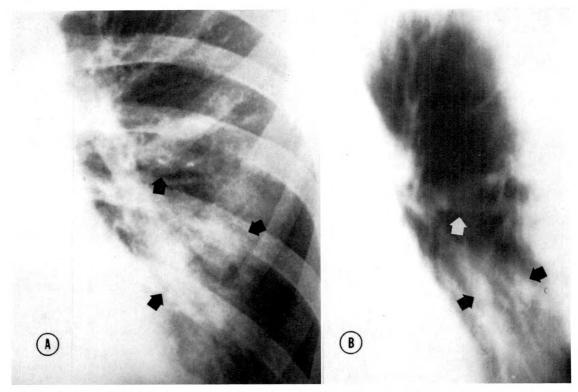


Fig. 1. Case I. (A) Infiltrative process in the lingula of left upper lobe. Several elongated densities (arrows) are seen within this process. (B) The densities are better demonstrated on the laminagram. Note their undulating borders. The white arrow points to a pair of densities forming a V with apex toward the hilus.

neoplasm, tuberculosis, pneumonia due to other causes, and Loeffler's syndrome.<sup>3,13</sup> It should be suspected whenever an abnormal shadow is found on the roentgenogram of an asthmatic patient. Its characteristic features should usually lead to the correct diagnosis.

#### CLINICAL ASPECTS

Mucoid impaction of the bronchi has no predisposition for any particular age group or sex. The usual symptoms are cough, fever, expectoration of plugs, chest pain, and hemoptysis. Asymptomatic cases are not uncommon. Episodes of impaction may be solitary or recurrent and migratory. The impaction will last indefinitely unless coughed up or mechanically removed.

#### REPORT OF CASES

Case 1. A 22 year old white male with a 5 year history of asthma entered the Minneapolis Veterans Hospital on August 8, 1954, for

evaluation of a pulmonary infiltrate. The infiltrate was discovered in June, 1954, and was associated with weakness, purulent sputum, and pleuritic pain. He was treated by his private physician. The symptoms improved, but the roentgen lesion persisted.

The patient was well developed and nourished. There were diffuse inspiratory and expiratory wheezes on chest ausculation. Sputum culture grew a few hemolytic streptococci and no acid-fast bacilli. The tuberculine test was positive (second strength PPD). The chest roentgenogram showed an infiltrative process in the lingula of the left upper lobe. Several elongated densities were noted within this process. A pair of the densities formed a V pointing toward the hilus (Fig. 1,  $\mathcal{A}$  and  $\mathcal{B}$ ).

The patient left against medical advice on August 13, 1954, but returned on January 4, 1955. The roentgen findings were unchanged. A bronchogram on February 14 (Fig. 2) disclosed occlusion of the inferior segmental bronchus of the lingula with a large, bulky, V-shaped density beyond. A branch of the superior segmental bronchus was also occluded, and shadows sug-

gesting bronchial casts were seen distal to this obstruction. On bronchoscopy, the mucosa was diffusely reddened and thickened, these changes being most intense at the orifice of the lingula division. Skin tests with histoplasmin, coccidiomycin and blastomycin were negative as were several sputum cultures for fungi. One of 10 sputa showed a few large, vacuolated, atypical appearing, acid-fast bacilli on concentrated smear; cultures were negative for *Mycobacterium tuberculosis*. There was a peripheral eosinophilia of 450–900 cells/culmm. A few eosinophils were found in the sputum.

A lingulectomy was performed on March 14, 1955. All bronchi of the resected specimen were dilated up to 2 cm. in diameter and filled with tubular plugs of greenish-gray, firm, friable material (Fig. 3, A and B). Many of the subsegmental bronchi entered directly into large abscess cavities containing yellowish pus. The small amount of intervening parenchyma was fibrotic. On microscopic examination the bronchial walls were destroyed and infiltrated with inflammatory cells, mostly lymphocytes. The abscesses were lined by a zone of macrophages with foamy cytoplasm and a well vascularized fibrous wall with round cell infiltration. The parenchyma was almost entirely replaced by necrotizing pneumonia and fibrosis. Section of the bronchial plugs revealed alternating layers of homogeneous, eosinophilic substance and nuclear debris, mostly from polymorphonucleocytes. A smear of the resected tissue showed acid-fast organisms of "rough and fragile appearance" which failed to grow out or infect a guinea pig. Culture of the tissue yielded Aspergillus fumigatus and anaerobic streptococci. No fungus was found on PAS stain of the tissue and the bronchial plugs.

A roentgenogram taken on discharge on April 11, 1955, disclosed a wedge-shaped area of mottled density in the right mid-lung field. This resolved without treatment by June 30, 1955. The patient was seen frequently by his private physician for bouts of "acute asthmatic bronchitis requiring the use of antibiotics" and was maintained on tedral and isuprel nebulization.

In October, 1962, atelectasis of the left upper lobe was discovered on a routine chest roent-genogram. On readmission to the Minneapolis Veterans Hospital on November 5, 1962, the patient gave a history of having coughed up about 6 rod-like plugs during the preceding 6 weeks. He further stated that plugs had been

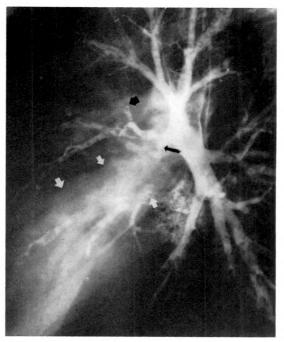


Fig. 2. Case I. Left lateral bronchogram (February 14, 1955). The inferior segmental bronchus of the lingula is occluded (long black arrow). Beyond the point of occlusion is a V-shaped density formed by a large upper limb (upper white arrows) and a small lower limb (lower white arrow). The short black arrow indicates occlusion of a branch of the superior segmental bronchus. Note shadows of mucoid impactions distal to it.

raised prior to his 1955 admission. There was generalized wheezing. The breath sound was slightly decreased over the left upper lobe area. Roentgenographically, the atelectasis appeared to have resolved by that time, but densities consistent with mucoid impaction were shown in the left upper lung field. A bronchogram (Fig. 4 A) demonstrated complete occlusion of the upper division of the left upper lobe bronchus and of several branches of the superior segmental bronchus of the lower lobe. Shadows of mucoid casts were clearly visible beyond the points of occlusion. The patient was treated intensively with heated glycero-saline by motor nebulization, isuprel inhalation, and tetracycline without improvement. Subsequently, pancreatic deoxyribonuclease (Dornovac, Merck, Sharp & Dohme) was administered for several days by positive pressure and, on one occasion, by direct bronchial instillation following bronchial lavage with normal saline, with expectoration of some brown sputum. Acetyl-cysteine (Mu-

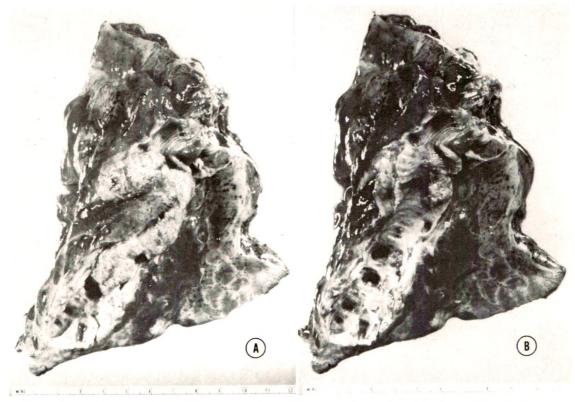


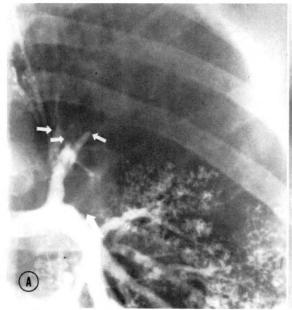
Fig. 3. Case I. Resected lingula of left upper lobe. (A) Mucoid impactions filling bronchi of the lingula.

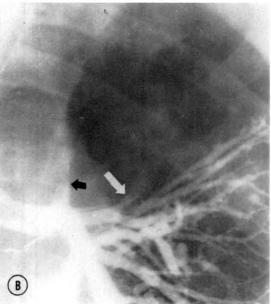
(B) Dilated bronchi after removal of the impactions.

comist, Mead Johnson) was then given by percutaneous intratracheal catheter and by intermittent positive pressure. On December 1, the second day of this treatment, the patient coughed up the first mucus plug since his readmission. On December 6, after production of more plug fragments, a bronchogram showed filling of the proximal portion of the upper division of the left upper lobe bronchus. The patient was sent home on leave at this time with instructions to continue acetyl-cysteine by nebulization. Many more plugs, some laminated and some hollow, were raised during this period. Another bronchogram (Fig. 4B) on January 3, 1963, revealed further opening up of the upper division of the left upper lobe bronchus, but now there was obstruction of the superior segmental bronchus of the lower lobe. Continued treatment was accompanied by production of additional plugs and thick brown sputum. A repeat left bronchogram (Fig. 4C) on March 19, 1963, disclosed almost complete filling of the superior segmental bronchus of the lower lobe. The apical-posterior segmental branch of the upper lobe remained occluded.

On June 18, 1963, following a week of productive cough, 2 round roentgenographic opacities were discovered in the right middle lobe area (Fig. 5A). The patient was again hospitalized and was given tetracycline, penicillin, and intensive acetyl-cysteine nebulization. The opacities disappeared within 10 days, leaving behind 2 round air spaces on the roentgenogram (Fig. 5B). The patient was kept on maintenance doses of acetyl-cysteine with occasional addition of antibiotics without further symptoms or changes as of February, 1965. In the meantime, the sweat chloride level was determined by iontophoresis using pilocarpine and found to be normal (right arm: 35 mEq/L, left arm: 36 mEq/L), and biopsy of several labial mucous salivary glands showed no abnormalities.9

Comment. This was an example of the recurrent, migratory and protracted nature of some cases of mucoid impaction. The roentgenographic findings were typical. The initial difficulty in diagnosis, centering on the exclusion of tuberculosis and bron-





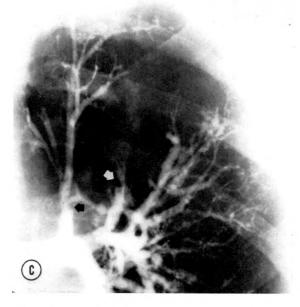


Fig. 4. Case I. Left bronchogram. (A) November 9, 1962. Occlusion of upper division of upper lobe bronchus (large arrow) and several branches of superior segmental bronchus of lower lobe (small arrows). Shadows of mucoid casts are visible beyond the points of occlusion. (B) January 3, 1963. Reopening of upper division of upper lobe bronchus and its anterior segmental branch. Persistent nonfilling of apical-posterior segmental branch (white arrow). The superior segmental bronchus of lower lobe is now occluded (black arrow). Note lumpy impactions distal to the points of occlusion and filling defects due to mucus. (C) March 19, 1963. The superior segmental bronchus of lower lobe is now filled with the exception of one branch (black arrow). Persistent occlusion of the apical-posterior segmental bronchus of upper lobe (white arrow).

chogenic carcinoma, was a common experience. The pathologic changes found in the removed lung tissue were in agreement with those described in the literature. 6,12 The apparent therapeutic response to acetyl-cysteine with bronchographic documentation was exceedingly interesting. A similar result has been reported by Webb. 16 The significance of the positive culture for aspergillus will be considered later.

Case II. A 49 year old nurse with a history

of severe childhood asthma was asymptomatic until 1958 when she had a bout of pneumonia. Since then the patient had had increasingly severe attacks of asthma in the spring and fall, usually associated with acute bronchitis. There was an allergic background in both the patient and her family.

A right carotid body excision was done on February 26, 1964, with marked relief of symptoms for 2 months. Her condition worsened thereafter. Despite bronchodilators, acetylcysteine, antibiotics, and short courses of steroids, the patient went into status asthmaticus

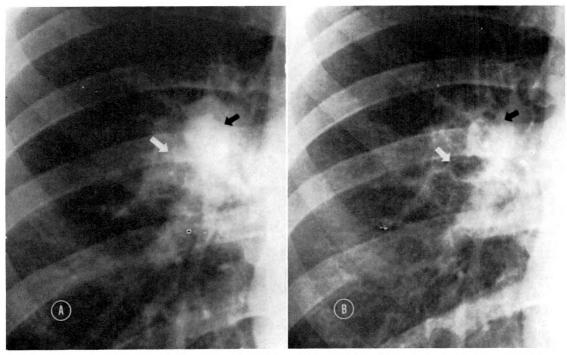


Fig. 5. Case I. (A) June 18, 1963. Two round densities (arrows) in right hilus representing impactions within the middle lobe. (B) June 28, 1963. Air spaces (arrows) representing dilated bronchi after evacuation of the impactions.

and became comatose in July, 1964. She was resuscitated with tracheal intubation and mechanical ventilation.

She was first admitted to the Minneapolis Veterans Hospital on August 4, 1964, in moderate respiratory distress. Examination revealed sinus tachycardia, obesity, and generalized wheezing on chest auscultation. There was a peripheral eosinophilia of 1,800 cells/cu.mm. Many eosinophils were found in the sputum as well. Repeated sputum cultures grew Pseudomonas. Acid-fast bacilli were not found. Cultures for fungi were contaminated.

The roentgen changes were typical of mucoid impaction of the bronchi. In the frontal view, a few round densities were seen in and near the right hilar region (Fig. 6, A and B). These were also noted on a roentgenogram made in 1958. Lateral laminagrams showed a V-shaped shadow having the appearance of a cluster of grapes in the superior segment of the right lower lobe (Fig. 7 A) and a round shadow in the right middle lobe. A bronchogram dated January 14, 1964, was reviewed. The lateral segmental branch of the right middle lobe bronchus was observed to be occluded. A round impac-

tion was seen immediately distal to the obstruction.

The patient's asthma improved on a regimen of bronchodilators, tetracycline, and large doses of steroids. Beginning September 8, 1964, acetyl-cysteine was given by intermittent positive pressure. This treatment was accompanied by postural drainage and back percussion. Lateral laminagraphy was repeated on October 1. The round density in the right middle lobe and the upper limb of the V-shaped density in the superior segment of the lower lobe were no longer demonstrated. A radiolucent defect had appeared within the remaining limb of the V, indicating partial evacuation of this impaction (Fig. 7 B). The patient was discharged on October 2, 1964. Follow-up roentgenograms through January, 1965, showed no change.

Comment. This case illustrates the persistence of mucoid impactions over a period of years. Only incomplete dislodgement was achieved despite vigorous treatment.

#### DISCUSSION

The true incidence of mucoid impaction

of the bronchi has not been determined. It is undoubtedly greater than the scanty literature would indicate.

The cause of mucus accumulation in a bronchus is not definitely known. Interference with its removal due to loss of ciliary action probably plays the most important role. According to Naylor, <sup>10</sup> shedding of the ciliated bronchial epithelium is a phenomenon that occurs almost exclusively in asthma, increasing considerably during attacks. Presumably, the longer the attack, the greater the likelihood that mucus plugging will take place. The extreme is represented by the fatal cases of status asthmaticus. Here, the 2 most constant postmortem findings are: (1) widespread detachment of

ciliated epithelium and (2) generalized mucus plugging of the bronchi.<sup>5</sup>

Mucoid impaction could conceivably result from production of an abnormally viscid mucus, as seen in mucoviscidosis. However, the normal sweat chloride values together with absence of any of the characteristic degenerative changes of the labial mucous salivary glands in Case I are strong evidence against an adult form of that particular disorder, at least in the homozygous form. An underlying constitutional defect of some kind is, nevertheless, suggested by the fact that relatively few asthmatics are afflicted by mucoid impactions, and those that are often have recurring episodes.

It is noteworthy that the bulk of cases of

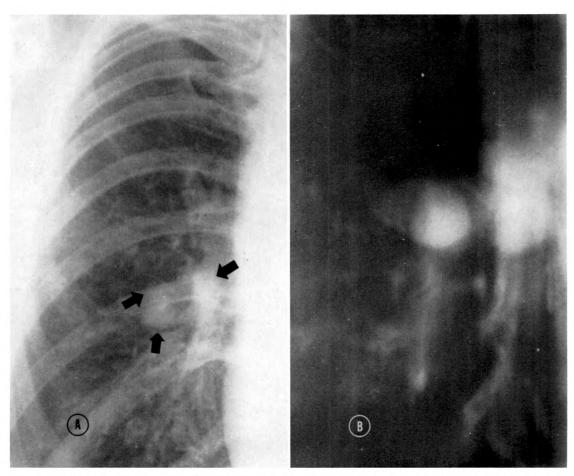


Fig. 6. Case II. (A) August 4, 1964. Round densities (arrows) in and near the right hilus, present since 1958. (B) Laminagraphic appearance of the same densities. They represent straight or oblique cross sections of mucoid impactions. Note the sharp outlines, the homogeneous opacity, and the round, oval or elliptic shape.

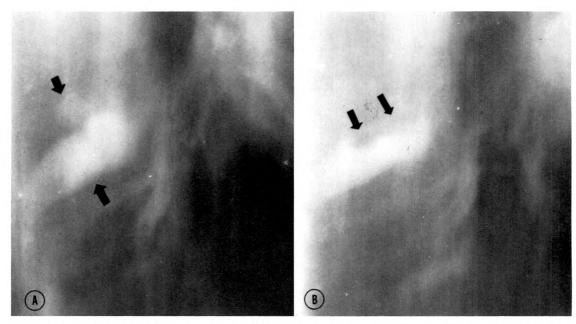


Fig. 7. Case II. Right lateral laminagrams. (A) Two impactions (arrows) forming a V in the superior segment of lower lobe. Note the undulating or scalloped borders causing a cluster-of-grape appearance. A single round density in the middle lobe was seen at another laminagraphic level (not shown). (B) Radiolucent defect (arrows) within an impaction after a fragment of it has been dislodged.

mucoid impaction has been reported by Shaw or his associates from Dallas, Texas. 6,12,13,14 This high incidence should perhaps be attributed to the increased awareness of this condition among the local medical profession rather than to any geographic or climatic influence.

There are reasons to believe that mucoid impaction may be a variant of plastic bronchitis. In this condition a cast is formed in a lobar or main bronchus, resulting in lobar or massive collapse. The etiology is unknown. Asthma is not a prominent feature although a history of preceding respiratory ailment is sometimes obtained. The cases of mucoid impaction presented by Smith and Clark<sup>15</sup> are closer to this variety. The syndrome usually associated with asthma, on the other hand, is characterized by predominantly subsegmental or segmental involvement and a more specific roentgen pattern. It is quite possible that the two are basically the same disorder. 15

An interesting relation exists between the allergic type of aspergillosis on the one hand, and asthma and mucoid impaction

on the other.<sup>1,4</sup> The fungus apparently may act as a persistent or recurrent allergen in the respiratory tract of asthmatic patients. It may also cause a sudden acute asthmatic attack in a previously normal person. Bronchial plugs may form and be coughed up in either instance. In some of the cases reported by Goldberg,1 the typical roentgen appearance of mucoid impaction is shown in the illustrations. More commonly, the picture is that of migratory segmental or lobar collapse. Aspergillus is cultured from the sputum, and mycelia are found in the plugs. 4 Immunologic studies, including tests for skin and bronchial sensitivity to aspergillus extract, support the allergenic role of the fungus.11 In Case I reported above, the positive aspergillus culture of the resected lung was thought to be etiologically insignificant, in view of the negative finding on PAS stain of the tissue and the plugs.

#### SUMMARY AND CONCLUSIONS

The pathologic, roentgenographic, and clinical aspects of mucoid impaction of the bronchi are described. The favorable out-

come of 2 cases treated with acetyl-cysteine is reported.

The pathogenesis of mucoid impaction and its relation to mucoviscidosis, plastic bronchitis and allergic aspergillosis are discussed.

Mucoid impaction should be suspected whenever an abnormal shadow is seen on the chest roentgenogram of an asthmatic. The roentgen diagnosis is, as a rule, not difficult.

S. H. Tsai, M.D. Department of Radiology Veterans Administration Hospital 54th Street and 48th Avenue, South Minneapolis, Minnesota 55417

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# ANGIOCARDIOGRAPHIC FINDINGS IN TRAUMATIC RUPTURE OF A BRONCHUS\*

REPORT OF TWO CHRONIC CASES

By ISRAEL STEINBERG, M.D.,† and LAURENCE MISCALL, M.D. NEW YORK, NEW YORK

ANGIOCARDIOGRAPHY is neither essential nor does it provide the definitive diagnosis of traumatic rupture of a bronchus. Rather, it furnishes valuable data regarding the degree of distortion of the great vessels, especially the state of the pulmonary circulation, in the affected and contralateral lung. By revealing a pulmonary artery, albeit hypoplastic, of the affected lung, it differentiates congenital absence of a pulmonary artery and agenesis of a lung from traumatic rupture of the bronchus. These data are illustrated by the 2 chronic cases of tracheal rupture herein reported.

#### REPORT OF CASES

Case I. A 44 year old Caucasian woman (N.Y.H. No. 474 741) was admitted on November 17, 1947, complaining of cough, expectoration, and dyspnea. These began in childhood and followed injury to the left anterior chest at the age of 10 years by falling cans of fruit which toppled from a shelf as she reached up for a can. Attacks of respiratory infection with expectoration of yellow-green sputum recurred for many years. Eight years prior to admission, she had large hemoptysis and, following this, progressive and increasing dyspnea on exertion developed.

Examination showed a well developed and well nourished woman in no distress. Dullness and absent breath sounds were present below the left scapula. The heart sounds were distant; no murmurs were heard. The blood pressure was 150/86 mm. Hg. The electrocardiogram showed normal sinus rhythm and right axis deviation suggestive of either right ventricular hypertrophy or shift of the heart. The roent-genogram of the chest showed the left hemi-

thorax to be contracted and smaller than the right. The trachea, mediastinum, and heart were markedly shifted into the left hemithorax (Fig. 1). Bronchograms on May 13, 1947, showed marked narrowing of the left main bronchus immediately below its origin (Fig. 2,  $\mathcal{A}$  and  $\mathcal{B}$ ). Angiocardiograms on May 20, 1947, revealed marked rotation of the cardiovascular structures into the left hemithorax. The main and right pulmonary arteries were normal in size, but the left pulmonary artery was small. The right pulmonary arterial system was unduly distended and reached into the left hemithorax (Fig. 3,  $\mathcal{A}$  and  $\mathcal{B}$ ).

At operation, on June 10, 1947, the left lung

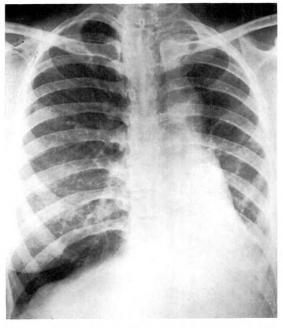


Fig. 1. Case 1. Frontal teleroentgenograms of the chest showing deviation of the trachea, mediastinum, and heart into the left hemithorax with marked overdistention of the right lung.

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<sup>\*</sup> From the Departments of Radiology and Private Surgery, The New York Hospital—Cornell Medical Center, New York, New York.

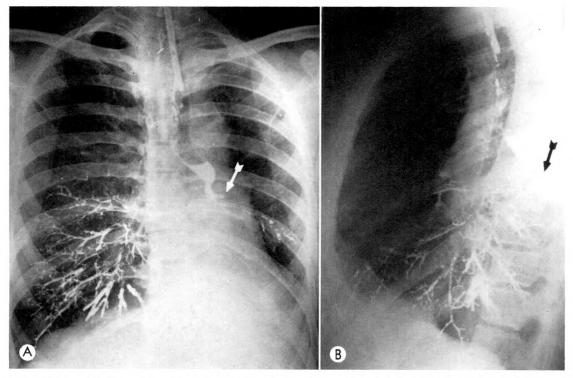


Fig. 2. Case I. (A) Frontal bronchogram showing abrupt closure of the left bronchus immediately below the carina (arrow). (B) Lateral bronchogram also showing the occluded left bronchus (arrow).

was found to be collapsed, unaerated, firm in consistency, and fixed to the posterior chest wall adjacent to the vertebral column. The left main bronchus was markedly stenosed beyond the carina. The right lung herniated into and almost completely filled the left hemithorax. The heart was rotated into the left chest and fixed to the posterior wall at the level of the ninth rib in the vertebral gutter. After inspection, the mediastinal hernia was reduced by pushing the right lung back into its proper position. The left lung and heart were freed from the posterior chest wall and a left pneumonectomy was done. The pericardium was opened and sutured to the undersurface of the sternum near its left border, restoring the heart to its regular position. A modified short rib thoracoplasty of the left upper ribs was performed in order to maintain the position of the heart. The patient was well for several hours following surgery but then died in shock. Permission for an autopsy was not secured.

Examination of the excised lung showed it to be 15×7×2.5 cm. in size. The trachea leading into it measured 1 cm. The peribronchial area was markedly indurated and fibrous and con-

tained two 2.5 cm. dilatations—saccular bronchiectasis. Other bronchi were cylindrical and contained pus. Microscopic examination revealed bronchiectasis with interstitial pneumonia.

CASE II. A 13 year old Negro boy, while hitching a ride on the back of a bus on December 25, 1950, fell off, and was run over by a car. He was rushed to a hospital where roentgenographic studies of the chest disclosed a left hydrothorax without fracture of the ribs. Thoracentesis of the left chest yielded blood and it was aspirated. Recurrent chest taps alleviated dyspnea; the patient improved and was discharged. However, he continued to be dyspneic and roentgenograms of the chest disclosed the trachea, mediastinum, and heart to be rotated into the left hemithorax. Bronchography showed occlusion of the left main bronchus I cm. below the carina. Angiocardiography on April 29, 1952, showed the cardiovascular structures rotated into the left hemithorax in the right anterior oblique position. The main and right pulmonary arteries were prominent. The left pulmonary arterial and venous circulation appeared

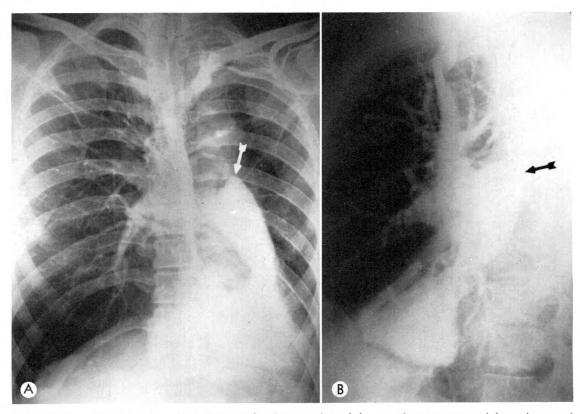


Fig. 3. Case I. (A) Frontal angiocardiogram showing rotation of the superior vena cava, right atrium, and ventricle into the left hemitherax in the position of the right anterior oblique view. The right pulmonary arterial branches are distended and also supply the herniated portion of the right lung which lies in the left hemithorax. Note the attenuated left pulmonary artery "on end" (arrow). (B) Lateral angiocardiogram also showing the great vessel and cardiac rotation. The left pulmonary artery (arrow) is small.

markedly attenuated, whereas the right lung vasculature was distended and even extended into the left hemithorax (Fig. 4).<sup>10</sup>

Thoracotomy revealed complete division of the left main bronchus about I cm. below the carina. The proximal and distal bronchial stumps of the left bronchus were completely sealed by scar tissue. Attempts were made to reinflate the atelectatic lung and restore it to a functioning state. When this failed, a left pneumonectomy was performed. The right lung was replaced into its proper position. The pericardium was opened and sutured to the undersurface of the sternum, restoring the heart to its regular location. Recovery was uneventful and the patient has been asymptomatic. The excised lung was small and surrounded by dense fibrous adhesions. The alveoli were atelectatic and without infection.

#### DISCUSSION

Notable reviews of acute and chronic

traumatic rupture of a bronchus have appeared in the surgical1,3,5-8,10,13-15 and roentgenologic<sup>4,9</sup> literature. These have stressed that the trauma producing tracheal rupture is usually severe and often causes immediate fatality. In Case 1, rupture of the left main bronchus followed injury to the thorax by heavy fruit cans; in Case II, the wheels of a car provided the trauma. Very few details of the accident were volunteered by the first patient, probably because of poor childhood recollection, but also because of fears that the hemoptysis might have been due to pulmonary tuberculosis. The second patient was also reluctant to discuss the events surrounding the injury, apparently because he felt guilty about stealing a ride. Hemothorax followed the chest trauma in Case II, but apparently it was not too severe or caused shock.

Conservative treatment—aspiration of the blood only—was used.

Both patients developed atelectasis of the affected lung causing it to shrink. To compensate for this, the opposite lung became overdistended and herniated across the mediastinum into the contralateral side. The trachea, mediastinum, and cardiovascular structures were displaced into the left hemithorax, creating a condition called fibrothorax11 (Fig. 1; and 2, A and B). Bronchograms in both cases showed stenosis of the left bronchus immediately below the carina (Fig. 2, A and B). Angiocardiograms showed the great vessels and cardiac chambers rotated into the left hemithorax, assuming the right anterior oblique position (Fig. 3, A and B; and 4). Both patients had closure of the left bronchial stumps and in each case, because of greatly thickened pleura, reinflation of the collapsed lung could not be accomplished. Although left pneumonectomy was successful in the first patient, it was probably complicated by hemorrhage which resulted in fatal shock. In the second patient, left pneumonectomy was curative. In the excised lung of the first patient,

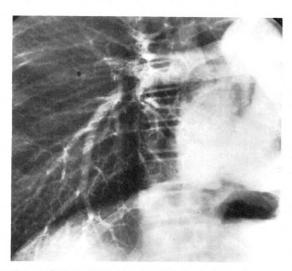


Fig. 4. Case II. Frontal, 9 by 9 inch, angiocardiogram showing the markedly distended right pulmonary arterial system supplying the lung which has also herniated into the left hemithorax. The cardiovascular structures are rotated into the right oblique position.

there was severe bronchiectasis and pneumonitis. In the younger patient, the lung was free of infection, and this may have been the reason for cure—excision having been made before a chronic, disabling, suppurative disease developed.

The angiocardiographic pattern of attenuated pulmonary circulation in rupture of a bronchus is different from that in agenesis of a lung and congenital absence of a pulmonary artery. In the latter conditions, although there is herniation of the lung into the contralateral hemithorax, a pulmonary artery of the affected lung is absent. Also, the pulmonary venous and bronchial arterial circulations are absent in both these instances. The bronchus is intact and present in the case of congenital absence of a pulmonary artery and entirely absent in agenesis of a lung. The bronchographic findings in both agenesis of a lung and traumatic rupture of a bronchus may sometimes appear to be similar because the constricted terminal end of the ruptured bronchus may be close to the carina and seem attenuated. On the other hand, angiocardiography, by showing an absent pulmonary circulation (arterial, venous, and bronchial), is definitive for diagnosis of agenesis of a lung.12

#### SUMMARY AND CONCLUSIONS

Two patients, a 44 year old woman with a left healed tracheal rupture incurred 34 years earlier, and a boy aged 13 years, with a left tracheal rupture of 2 years' duration, had angiocardiographic studies. In both, the great vessels and cardiac chambers were rotated into the left hemithorax in the position of the right oblique view. The pulmonary circulation of the right lung was markedly distended and reached into the left hemithorax—creating the condition known as fibrothorax. The left pulmonary arterial and venous circulations were patent but markedly attenuated.

In both cases, the pleura was dense and the tracheal and pulmonary ends of the ruptured bronchus were sealed off by fibrous tissue, making reinflation of the left lung impossible. Left pneumonectomy with replacement of the right lung and heart into their proper positions was successful in both cases but only the younger patient survived, probably because of his age, absence of infection in the atelectatic lung, and the shorter duration of the disease. The older patient who had had advanced bronchiectasis for many years died postoperatively of shock.

Since surgical restoration of the ruptured bronchus is lifesaving and prevents infection and atelectasis, any technique providing information regarding the cardiovascular system is important. For this reason, angiocardiography is recommended. It can also differentiate agenesis of a lung and congenital absence of a pulmonary artery from rupture of a bronchus—all of which have similar appearances in the conventional roentgenogram. However, in congenital pulmonary malformations, there usually is no history of trauma. Because 2 patients were reluctant to disclose the details of their accidents, angiocardiography proved especially valuable in the differentiation of bronchial rupture from congenital absence of a pulmonary artery or lung.

Israel Steinberg, M.D. The New York Hospital—Cornell Medical Center 525 East 68th Street New York, New York 10021

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#### FAT EMBOLISM\*

#### ROENTGENOGRAPHIC PATHOLOGIC CORRELATION IN 3 CASES

By THOMAS J. BERRIGAN, Jr., M.D., EDWARD W. CARSKY, M.D., and E. ROBERT HEITZMAN, M.D.

SYRACUSE, NEW YORK

CLINICAL fat embolism was first described in 1862, 18 and since then numerous articles have been written on the subject. However, the roentgenographic findings in fat embolism have received little attention.

Scuderi, in 1941, injected fat intravenously into dogs and demonstrated roentgenographically bilateral diffuse pulmonary densities. Maruyama and Little, in the only article on this subject in the radiologic literature, presented chest roentgenograms of 3 patients with clinically diagnosed pulmonary fat embolism. All of these patients recovered.

In a  $2\frac{1}{2}$  year period at two hospitals of the Upstate Medical Center, 6 cases of severe fat embolism were encountered. It is the purpose of the authors to review briefly the clinical course of this syndrome and to correlate the roentgenographic patterns with necropsy findings in 3 of these 6 patients.

#### ETIOLOGY

Fat embolism has been described in a variety of both traumatic and nontraumatic illnesses, but most authorities agree that clinically significant fat embolism is seen as a result of severe injury to soft tissues and bone, particularly with fractures of the shafts of the femora and the tibiae. Although there is some experimental evidence to suggest that physiochemical alterations in the blood of injured patients play a role in the development of fatty emboli, 5,6 the clinical significance of these changes is not yet known. Still generally accepted is Gauss's1 theory of etiology which states that after local injury to bone and soft tissue, intracellular fat globules are released

and subsequently enter torn and gaping veins through which they then pass proximally to the lungs. Intralymphatic intravasation is probably less important. These large chylomicrons vary in size from 5 to 40 μ in diameter and are much larger than the normal circulating fat globules. Because of their large size they become temporarily arrested in the alveolar capillaries where their detrimental effect upon the pulmonary parenchyma probably results from a variety of factors: (1) direct embolic effect producing local ischemia, (2) alteration of the viscosity of the blood, and (3) the toxic effect of hydrolyzed fatty acids upon the alveolar membranes. Some fat globules, however, do pass unhydrolyzed into the left side of the heart and are distributed throughout the systemic circulation.

#### INCIDENCE

The reported incidence of fat embolism after injury is varied. Sevitt14 found pulmonary fat embolism in 89 per cent of posttraumatic deaths and systemic emboli in 24 per cent. It has been shown experimentally that some degree of pulmonary fat embolism regularly follows injury to the long bones. Vance16 found pulmonary fat emboli in 43 of 48 patients dying in the first week after fractures of the lower extremities. In 30 of these patients, the degree of fat embolism was described as moderate or severe. Scully<sup>13</sup> reported similar figures in fatal Korean War casualties, but he doubted the clinical significance of these emboli. Glas et al.2 in a clinical study reported an incidence of 52 per cent following moderate or severe trauma where the diagnosis was based solely upon the demonstra-

<sup>\*</sup> From the Radiological Services of the Crouse Irving Hospital and the Syracuse Memorial Hospital, Syracuse, New York, and the Radiology Department of the State University of New York, Upstate Medical Center, Syracuse, New York.

tion of fat in the urine. They concluded that fat embolism is a condition of great importance and that there probably are many cases with mild symptoms which go unrecognized.

#### CLINICAL FINDINGS

There is usually, although not always, a 24 to 48 hour latent period after the injury before symptoms become manifest. The pulmonary syndrome generally appears first. The patient develops dyspnea, cyanosis, tachypnea with an accompanying cough, pyrexia and tachycardia. Hemoptysis, although previously reported as rare, occurred in 5 of our 6 patients and pulmonary hemorrhage was a prominent feature of the pathologic findings. Diffuse rhonchi and rales are present and occasionally a pleural friction rub is heard.

Symptoms secondary to systemic embolism usually appear after the pulmonary manifestations. Although systemic emboli are distributed throughout all organs in proportion to the cardiac output, cerebral emboli predominate in causing the clinical syndrome of systemic embolism. In the brain, the functions of the white matter appear to be particularly impaired by the emboli and resultant ischemia. The major cerebral manifestations are headache, apprehension, irritability, delirium, stupor, convulsions and finally coma. Which of these states predominates will depend on the severity of the embolism. Localizing signs are usually absent.

A petechial rash, more pronounced on the neck and anterior chest wall, often appears. This rash, along with pulmonary and cerebral effects, makes up the characteristic triad of the classic syndrome of traumatic fat embolism. The majority of patients undoubtedly recover with few if any sequelae. The appearance of coma, however, signifies a poor prognosis.

#### DIAGNOSIS

Besides the classic syndrome resulting from pulmonary, cerebral and cutaneous emboli, there are other clinical and laboratory aids available because of generalized systemic embolism.

Fat in the urine can be readily detected by either Sudan staining or by the so-called "sizzle" test of Scuderi.<sup>12</sup>

Although these patients also have considerable fat in their sputum, the practical value of staining for it is limited because it has been demonstrated that the sputum of one-third of normal individuals contains fat.<sup>2</sup>

Fat emboli occur in the retinal vessels and ophthalmoscopic examination may show retinal petechiae and occasionally fat globules in the retinal vessels.

Although coronary emboli undoubtedly occur, no specific electrocardiographic abnormalities have been described. Minor S-T wave changes, with evidence of right heart strain may be noted.

Abnormally large fat globules in the blood can be demonstrated by special staining techniques.8

#### REPORT OF CASES

CASE I. L.S., a 23 year old female, sustained multiple abrasions and a fracture of the right femoral shaft in an automobile accident. Twelve hours after admission, she became confused, febrile, cyanotic and tachypneic. Shortly thereafter coma ensued. At 24 hours, petechiae were noted on the conjunctivae, neck and anterior chest wall. A tracheostomy was performed and copious bloody tracheal secretions developed. Fat was demonstrated in the urine by Sudan staining. A chest roentgenogram (Fig. 1) showed bilateral parenchymal densities. The patient was given heparin and intravenous alcohol in an attempt to hydrolyze the fat. The coma progressively deepened, however, and she died approximately 80 hours after injury. Autopsy demonstrated heavy lungs (1,270 and 1,170 grams) which were deep maroon in color. A moderate amount of pink frothy fluid was present in the bronchi. Microscopically, the alveolar spaces were distended with blood (Fig. 2). Flameshaped hemorrhages were demonstrated throughout most of the cerebral hemispheres. The lungs and kidneys demonstrated abundant intravascular fat by special staining.

CASE II. J.B., a 20 year old male, sustained

fractures of the left femur, fibula, humerus and ulna in an automobile accident. Three days after admission he became dyspneic and febrile, and 24 hours later confusion and stupor ensued. Petechiae were noted on the neck and anterior chest wall. A chest roentgenogram (Fig. 3) demonstrated diffuse bilateral pulmonary densities. He was given heparin but became comatose and died 5 days after his accident. At autopsy, the lungs weighed 1,650 and 1,350 grams and were deep purple in color. There was unclotted blood in the bronchial tree and hemorrhage in the alveolar spaces. Special stains demonstrated fat in the alveolar and glomerular capillaries. The brain was not examined.

Case III. H.St.P., a 10 year old obese male with progressive muscular dystrophy, had surgery under Fluothane anesthesia for bilateral equinovarus deformities. With tourniquets on the lower extremities, bilateral heel cord resections and transplantation of the tibialis muscles were done. Immediately postoperatively he became cyanotic and restless. The next day he was incoherent. Hemoptysis, dyspnea and tachypnea developed. The hemoptysis was ac-

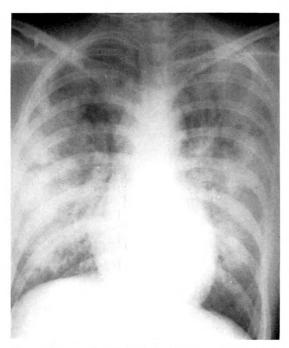


Fig. 1. Case 1. Anteroposterior roentgenogram made with a portable unit approximately 24 hours after injury shows marked diffuse pulmonary density, slightly more marked in the lateral periphery of the lungs.

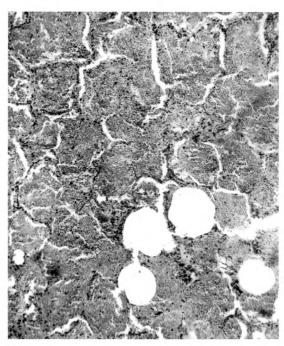


Fig. 2. Case I. Microscopic section of the autopsied lung showing alveoli markedly filled with blood.

companied by a drop in his hematocrit to 34 per cent from a preoperative level of 42 per cent. A chest roentgenogram (Fig. 4) demonstrated bilateral confluent infiltrates. In spite of extensive



Fig. 3. Case II. Anteroposterior roentgenogram made with a portable unit approximately 4 days after injury shows moderate to marked diffuse density fairly evenly distributed with slightly greater density in the lateral periphery.

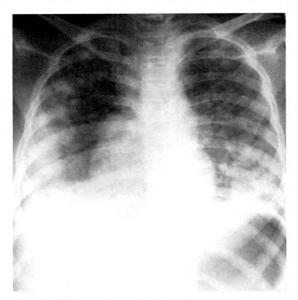


Fig. 4. Case III. Anteroposterior roentgenogram made with a portable unit approximately 24 hours after surgery shows diffuse pulmonary abnormality but with much greater involvement in the lateral periphery of the lungs.

supportive measures, the patient developed shock and died 65 hours postoperatively. At necropsy, both lungs were dark purple and moderate hemorrhage was present in the bronchi. Microscopically, there was extensive edema and hemorrhage in the alveoli. Fat was demonstrated in both lungs and kidneys.

Interestingly, and possibly related to the etiology of the fat embolism in this case, all of the examined muscles were extensively replaced with fat, a change secondary to the muscular dystrophy. There was also fatty metamorphosis of the liver.

#### ROENTGENOGRAPHIC FINDINGS

The chest roentgenogram may be entirely normal if the degree of fat embolism is not severe. Only one-eighth of the patients of Glas *et al.*<sup>2</sup> who demonstrated lipuria had abnormal roentgenograms. Severe pulmonary fat embolism occurred in our patients and the roentgenographic patterns presented were those of diffuse bilateral parenchymal densities resembling pulmonary edema but accompanied by a normal sized heart and no pleural effusion.

These patterns were similar to those previously reported<sup>5,7,11</sup> except that in our fatal cases the changes were more marked in the lateral peripheral portions of the lung fields with less abnormality noted in the perihilar regions. The apices tend to be less involved. This distribution is at variance with that reported by Maruyama and Little7 who indicated a perihilar distribution in their nonfatal cases. The reason for this discrepancy in distribution is not readily explained. The pulmonary vessels and right ventricular outflow tract are difficult to evaluate as these films are invariably exposed at short distances with portable equipment. Vascular congestion does not appear to be a prominent finding, however. Our 3 autopsied cases developed symptoms immediately, 12 hours and 3 days, respectively, after trauma. Roentgenograms made following the onset of symptomatology showed characteristic findings in each case. It appears, therefore, that the development of roentgenographic findings in severe cases may range between a few hours and several days.

#### PULMONARY PATHOLOGY

Postmortem studies were done on the 3 patients reported here and the pulmonary findings have been uniformly similar. Sanguineous secretions were present in the tracheobronchial tree and grossly the lungs were reddish-purple in color. The lungs were heavy, usually weighing 1½ to 3 times normal. Microscopically, the most striking finding was extensive intra-alveolar hemorrhage with lesser amounts of edema fluid associated. Fatty vacuoles were demonstrated in alveolar capillaries and alveoli. The pulmonary vessels were normal and no patient had pleural effusion. Systemic emboli were demonstrated in all cases. It is apparent that the roentgenographic findings are due to intra-alveolar hemorrhage and edema which are probably secondary to the ischemic and toxic effects of the fat and the resultant endothelial anoxia.

#### SUMMARY AND CONCLUSIONS

- 1. The clinical features of post-traumatic fat embolism are briefly reviewed.
- 2. The chest roentgenograms of 3 patients who died from fat embolism are presented and have been correlated with necropsy findings.
- 3. Traumatic fat embolism, although uncommon, will probably be seen with greater frequency as the number of automobile accidents increases.
- 4. The diagnosis of fat embolism frequently can be first suggested by the radiologist when confronted with a rather typical chest roentgenogram in a patient who has recently sustained a fracture of one or more of the long bones.

E. Robert Heitzman, M.D. Department of Radiology Upstate Medical Center 750 East Adams Street Syracuse, New York 13210

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#### COMPLICATIONS FOLLOWING LYMPHOGRAPHY WITH PARTICULAR REFERENCE TO PUL-MONARY OIL EMBOLIZATION\*

By MELVIN E. CLOUSE, M.D.,† JONAS HALLGRIMSSON, M.D.,‡ and DALE E. WENLUND, M.D.§

BOSTON, MASSACHUSETTS

LYMPHOGRAPHY is a relatively new technique used in radiology to outline disease processes and gross pathologic anatomy in lymphoid structures with oily contrast material. It has been most useful in studying the retroperitoneal area, where disease involving the lymphatic system may be extensive yet undetectable by palpation, urography, or inferior vena cavography.

Since the technique was described by Kinmonth<sup>11</sup> in 1952, a large number of papers has appeared correlating the roentgenographic appearance of disease in the lymphatic system with the gross and microscopic pathology to assess the usefulness of this procedure. Present evidence indicates that lymphography is most helpful in evaluating the treatment and staging of lymphoma,<sup>2</sup> completeness of the Wertheim procedure 7,12 and retroperitoneal4,15 lymph node dissections, and response of the lymph nodes to irradiation. The technique is less useful in determining the extent and presence of lymph node metastases since (1) completely replaced lymph nodes will not be visualized, (2) metastatic deposits in lymph nodes must be relatively large before a filling defect is visible roentgenographically, and (3) fat, fibrosis, and nonfilling of normal lymph nodes simulate malignant filling defects.

In almost all examinations involving the injection of an oily contrast medium, there is danger of venous intravasation leading to pulmonary embolism. This complication has occurred following hysterosalpingog-

raphy, <sup>9</sup> urethrography, <sup>17</sup> and myelography. <sup>10</sup> It is particularly likely to occur when an oily medium is injected into the lymphatics. Little, however, has appeared in the literature concerning this or other complications of injecting oily contrast material into the lymphatics. In the following pages we shall present the complications associated with 108 lymphographic procedures, with particular reference to diffuse pulmonary changes.

#### METHOD AND MATERIALS

After a 10 minute surgical preparation consisting of cleansing with Phisohex, ether, 37 per cent iodine solution, and then alcohol, the skeletal lymphatics are visualized by injection of the first two web spaces of the feet intradermally and subcutaneously with a mixture of 0.5 ml. of 11 per cent patent blue violet dye and 0.5 cc. of 2 per cent lidocaine hydrochloride. The dye rapidly enters the lymphatics. The skin on the dorsum of each foot is anesthetized with 2 per cent lidocaine hydrochloride and a dye-filled lymph vessel is exposed by a surgical cut-down and punctured with a 27 gauge needle tip attached to a 20 gauge polyethylene tube. Approximately 8 cc. of ethiodol or chlorophyll-ethiodol (an ester of poppy seed oil containing 37 per cent iodine) is injected into the exposed lymph vessel of each extremity with a constant infusion, at the rate of 0.136 ml. per minute. Immediately after the injection has begun, roentgenograms are made to exclude extravasation.

† Clinical and Research Fellow in Radiology, Massachusetts General Hospital.

<sup>\*</sup> From the Departments of Radiology and Pathology, Massachusetts General Hospital and Harvard Medical School. This paper was supported in part by USPHS Grant No. CST-155-64.

<sup>‡</sup> Assistant in Pathology, Harvard Medical School and Clinical Fellow in Pathology, Massachusetts General Hospital. § Resident in Radiology, Massachusetts General Hospital.

Roentgenograms of the abdomen are taken on completion of the injections for examination of the vessels, and 24 hours later for lymph node detail. Plain roentgenograms of the chest reveal the presence or absence of pulmonary oil embolization. The temperature is recorded routinely every 4 hours to determine febrile response.

#### COMPLICATIONS

1. Fever and Pulmonary Changes Following Oil Embolization. In 5 of our series of cases, spiking fevers of 101° to 104° F. developed within 6 hours following lymphography. A routine chest roentgenogram 12 hours after injection in these cases demonstrated diffuse oil emboli, and 36 hours after injection soft, diffuse, moderately discrete, linear-nodular densities were present throughout both lungs. In 4 patients the fever subsided after 24 to 48 hours but the linear-nodular pattern persisted for 3 to 9 days, with gradual spontaneous clearing. There was no clinical or roentgenographic evidence of sequelae 16 months after the examination.

Case I. A 42 year old female entered the hospital with epidermoid carcinoma of the vulva and questionable regional lymph node metastases but no evidence of pulmonary disease (Fig. 1). A lymphogram failed to demonstrate filling defects in the lymph nodes. Ap-

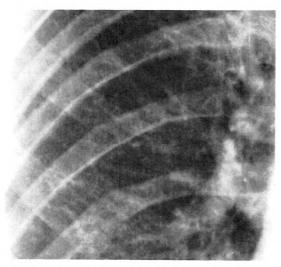


Fig. 1. Heart and lungs normal.

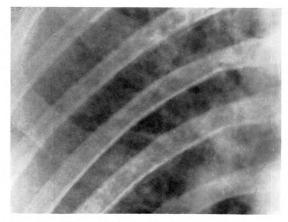


Fig. 2. Right upper lung field 48 hours following injection. Note diffuse soft linear-nodular densities.

proximately 6 hours after injection, the temperature was 102° F. The patient had slight dyspnea but no cyanosis, cough, hemoptysis, or chest pain. She experienced daily temperature elevations gradually decreasing to normal over the next 4 days.

A chest roentgenogram 12 hours after injection revealed diffuse oil emboli, and 48 hours after injection, soft moderately discrete, linear-nodular densities were demonstrable throughout both lungs (Fig. 2). Cultures of blood, sputum, and urine revealed no growth. The white blood cell count rose from 10,000 to 13,000.

Symptoms were not severe enough to warrant the use of steroids, and the patient felt well 4 days later even though the pulmonary densities persisted for another 5 days before clearing (Fig. 3).

CASE II. In a second case, pulmonary changes were accompanied by severe systemic symptoms requiring steroids. The patient, a 27 year old male with known seminoma who had previously received radiation therapy to the right chest wall and para-aortic and iliac lymph nodes, was admitted for evaluation of the retroperitoneal lymph nodes. An area of radiation fibrosis was present in the right mid-lung field. Six hours after the injection, the temperature spiked to 102° F., but it was normal the following morning and the patient was discharged even though there was roentgenographic evidence of oil emboli. He was readmitted 7 days later with a history of daily temperature elevations of 101° to 103° F. since discharge, drench-

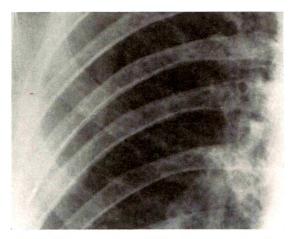


Fig. 3. Right upper lung field 9 days after injection. There is clearing of the nodular densities.

ing night sweats, a cough productive of gray mucoid blood-tinged sputum, and dyspnea on exertion to a few feet.

He was acutely ill, febrile, and cyanotic on this second admission, and could speak only for a few minutes before he became dyspneic. His white blood cell count was 7,300 with a normal differential count, hemoglobin 12 gm. per 100 ml., CO<sub>2</sub> 31 milliequivalents per liter, PCO<sub>2</sub> 34 millimoles per liter, blood pH 7.54, and SGOT (serum glutamic oxalic transaminase) 46. Cultures of urine, blood, and sputum revealed no growth. Chest roentgenograms showed diffuse soft linear-nodular densities throughout both lungs.

Cortisone (100 mg.) was given intravenously because of the severe dyspnea, cyanosis, lack of evidence of an infection, and the possibility of a reaction to the contrast material. Within 6 hours the temperature was normal and the patient was no longer dyspneic or cyanotic. Chest roentgenograms at that time revealed complete clearing of the nodular densities. There was no roentgenographic or clinical evidence of permanent change 20 months after the examination.

2. Oil Embolization without Pulmonary Changes. Roentgenographic evidence of oil emboli occurred in 20 cases, without associated fever, cough, chills, pleuritic chest pain, hypotension, or cyanosis. The oil cleared spontaneously in about 7 days and there was no roentgenographic or clinical evidence of sequelae 3 to 36 months after

the examination. There was no increase in the incidence of oil emboli associated with lymphatic obstruction, as reported by Bron et al. However, in cases with obstruction the injection was terminated when this became apparent, and most patients had received less than 16 cc. of contrast medium.

- 3. Fever. Fever occurred as the only complication in 5 cases and was occasionally accompanied by chills. The patients all responded to symptomatic therapy, and the temperature returned to normal in 3 to 4 days. Antibiotics were not necessary.
- 4. Wound Infections. There were 2 wound infections which healed with antibiotics and warm saline soaks. In another patient with lymphedema and pruritus, an abscess developed on the upper medial aspect of the thigh 7 days after injection, requiring surgical drainage, antibiotics, and warm saline soaks. Whether this was a direct result of the procedure is not known, since the legs were edematous, with excoriations from scratching before the examination.
- 5. Lymphangitis. In I case fever and lymphangitis occurred, with typical red streaking of the left leg, 2 days after injection, but this cleared with systemic antibiotics.
- 6. Delayed Wound Healing. Wound healing was delayed in 1 patient, probably due to undermining of the skin in searching for a suitable lymphatic vessel.
- 7. Lymphatic Rupture and Extravasation. In 2 patients with bilateral lymphedema and lymphatic obstruction in the pelvis, there was rupture of lymphatics in the upper thigh with extravasation of contrast material from the lymph vessels into the surrounding tissue.

#### PATHOLOGY

Guinea Pig Lungs. To study the pulmonary reaction to contrast material and its rate of elimination from human lungs, 5 guinea pigs weighing 0.4 kg. to 0.5 kg. were given 0.1 cc. ethiodol intravenously. The presence of ethiodol in the lungs was confirmed roentgenographically, and the ani-

mals were sacrificed 1 hour to 32 days post injection.

The contrast material was no longer visible roentgenographically after 12 days, but histologic examination demonstrated a considerable amount even after 32 days.

Within 24 hours there was extravasation of serum and lipid material into the alveoli (Fig. 4), surrounded by large numbers of neutrophils and lymphocytes (Fig. 5). The adjacent blood vessels also contained the same lipid material which, with brilliant cresyl blue and silver nitrate stain, proved to be ethiodol. Histiocytes were present on the second day and at the end of 8 days (Fig. 6) these predominated over the acute inflammatory cells. Foreign body giant cells were also present by the eighth day and oil granulomas were common (Fig. 7). Eosinophils were never prominent.

The acute inflammatory response gradually regressed and within 32 days there was clearing of most of the alveolar exudate and lipid material; the alveolar walls, however, remained thickened by swelling and proliferation of alveolar lining cells and capillary endothelium. The remaining oil at this time was present in the lumen of blood vessels scattered throughout the lungs, and in a few oil granulomas.

Human Lungs. Six patients died of causes unrelated to lymphography 1 to 33 days

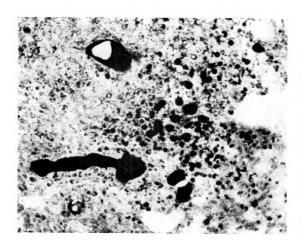


Fig. 4. Photomicrograph (X290) of guinea pig lung I day following injection of ethiodol. Note oil in blood vessels and alveoli.

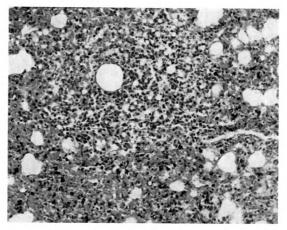


Fig. 5. Photomicrograph (X290) of guinea pig lung I day after injection of ethiodol. Acute inflammatory infiltrate surrounding globules of oil (clear spaces).

following the injection. In 4 who died after 3, 11, 27, and 33 days, ethiodol could still be demonstrated in pulmonary arterioles and capillaries. In 3 of the 6, who died at 11, 30, and 33 days, there was a marked reaction of endothelial and histiocytic cells within the lipid-containing vessels. A small oil granuloma was seen in 1 patient who died 11 days after injection (Fig. 8). In human lungs no other changes were present which could be related to the oily contrast material. Most of them showed small nonspecific areas of bronchopneumonia not anatomically related to the lipid material,

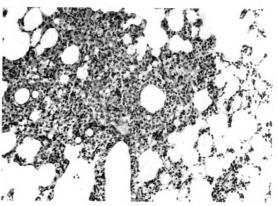


Fig. 6. Photomicrograph (X255) of guinea pig lung 2 days after injection of ethiodol. Histiocytes now predominate over lymphocytes and neutrophils. Oil is seen as clear spaces within infiltrate.

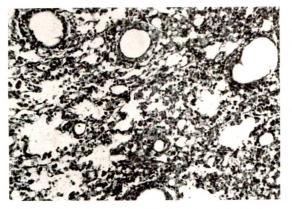


Fig. 7. Photomicrograph (X255) of guinea pig lung 8 days after injection of ethiodol. Many oil granulomas are seen as clear spaces surrounded by giant cells and large histiocytes.

prominent alveolar lining cells, and a few microthrombi.

Human Lymph Nodes. Lymph nodes from our surgical specimens showed pronounced sinus histiocytes and reticuloendothelial hyperplasia. These changes were present I day after injection. Foreign body giant cells were present the second day and were markedly prominent within 5 days. From the first day after injection, eosinophils were present in significant numbers in all lymph nodes containing contrast material. The largest number appeared near the injected material and in some instances lined the surface of the vacuoles along the histiocytes and giant cells (Fig. 9). Lymph

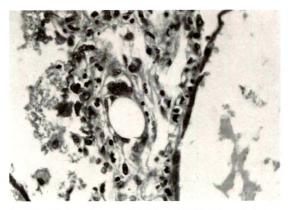


Fig. 8. Photomicrograph (X725) of human lung 11 days after lymphography. Oil granuloma represented by a clear space with surrounding foreign body giant cells.

nodes free of contrast material did not contain eosinophils or giant cells but showed only moderate reticuloendothelial hyperplasia and reactive germinal centers.

Extravasation of contrast material was infrequent and mostly in lymph nodes which had been partially replaced by fat. The extravasated contrast material caused an acute inflammatory reaction, with necrosis of adipose tissue. (Only small areas of necrosis and acute inflammation were seen in normal lymphoid tissue.)

#### DISCUSSION

Bron and his associates,¹ who reported on oil emboli in lymphangiography in 1963, observed roentgenographic pulmonary oil embolization in 55 per cent of 44 cases and noted an increased incidence with lymphatic obstruction. Schaffer *et al.*¹6 made a similar observation in 17 per cent of 144 cases, but by using I¹³¹-labelled ethiodol, demonstrated that it probably occurs in almost every examination.

Oil embolization generally does not cause pulmonary symptoms, although in some patients mild pyrexia may develop and

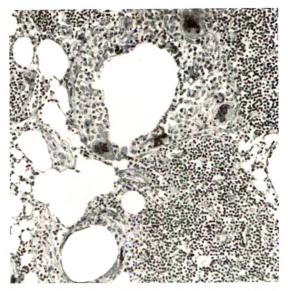


Fig. 9. Photomicrograph (X210) of human lymph node after injection of ethiodol. Note an infiltrate containing large numbers of eosinophils, as well as histiocytes and foreign body giant cells surrounding a vacuole of ethiodol (clear space).

roentgenographic stippling may be apparent in the lungs, due to the oil in pulmonary vessels. In this series, 20 patients had roentgenographic evidence of oil embolization but without even mild symptoms.

Severe acute symptoms have been observed. Schaffer and his associates<sup>15</sup> reported a case in which pulmonary infarction developed after the injection of 35 ml. of oily contrast medium. Fuchs, in a series of 20 patients, had 2 with lung infarction and 2 who suffered cardiovascular collapse after the injection of 25 ml. of ultra-fluid lipiodol. In 2 of Bron and co-workers' patients acute severe symptoms developed, with hypotension, cyanosis, dyspnea, and pleuritic chest pain. Both had pre-existing pulmonary disease: one atelectasis and the other severe emphysema. Gough et al.6 state that acute pulmonary symptoms are proportional to the amount of oil reaching the lung and to underlying lung pathology because oil emboli may further reduce respiratory function. Schaffer<sup>14</sup> has seen a patient who developed asthma during the injection and questioned allergy.

A death following lymphography has been recorded by Desprez-Curely et al.<sup>3</sup> after the injection of 25 ml. of ultra-fluid lipiodol in a 30 kg. child. The fatality was attributed to the presence of contrast material in the lungs. Nelson et al.<sup>18</sup> reported death, attributed to cerebral oil embolization, in a 57 kg. female after the injection of 40 ml. of ethiodol.

In addition to roentgenographic evidence of pulmonary oil emboli, 5 patients exhibited soft, moderately discrete nodular densities in a linear pattern throughout both lungs. In 4 patients symptoms were mild and there was gradual spontaneous clearing of the lungs within 3 to 9 days. In I patient symptoms were severe with dyspnea and cyanosis. The symptoms and roentgenographic changes cleared rapidly with steroids.

The pathology underlying these pulmonary changes is obscure. It is probably not related to pre-existing lung disease since only I patient had roentgenographic evi-

dence of this—a small area of radiation fibrosis. It cannot be attributed to bacterial pneumonitis because cultures of blood and sputum were negative, the nodular densities did not increase in size or become confluent, and there was no exacerbation with steroids.

The pulmonary changes may represent a local allergic response to the contrast medium. Marked infiltration of eosinophils in the lymph nodes and the immediate clinical response of I patient to steroids would support this theory, although the absence of eosinophils in sections of human and guinea pig lungs does not favor this.

The pulmonary changes probably represent an acute inflammatory response directly related to the irritating effects of the contrast medium as observed in the guinea pig lungs, the amount reaching the lungs, and individual host response because (1) the volume retained by the lymph nodes may vary considerably even though equal amounts were injected into the lymphatics; (2) many patients showed marked oil embolization without the development of pulmonary changes; and (3) a rapid clinical response to steroids would be expected.

Schaffer et al.16 reported no evidence of oil in lungs examined at autopsy 60 days injection; however, significant amounts of oil were observed in our cases after 33 days. Although no chronic inflammatory or fibrotic changes have been reported, present evidence suggests that ethiodol is a strong tissue irritant which may remain in the lungs for some time. With continued use of the procedure, chronic pulmonary changes may be observed, and for this reason we suggest longterm follow-up and careful selection of patients for lymphography.

#### SUMMARY

The complications resulting from 108 lymphographic examinations have been reviewed, with particular reference to unusual pulmonary changes following oil embolization, observed in 5 cases.

The microscopic pathologic changes seen

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in guinea pig lungs after the intravenous injection of ethiodol have been described to explain the presence of soft, moderately discrete linear-nodular densities observed in human lungs following lymphography. These roentgenographic changes in human lungs appear to be related to: (I) an inflammatory reaction to the contrast material; (2) volume of contrast medium reaching the lung; and (3) individual host response.

Melvin E. Clouse, M.D. 5209 Morley Fort Worth, Texas

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#### DIFFUSE BRONCHIOLECTASIS WITH MUSCULAR HYPERPLASIA ("MUSCULAR CIRRHOSIS OF THE LUNG")

## RELATIONSHIP TO CHRONIC FORM OF HAMMAN-RICH SYNDROME

By HANS KUISK, M.D., D.Sc.,\* and JOSE S. SANCHEZ, M.D.†
MINNEAPOLIS, MINNESOTA

RECENTLY, 3 cases came to our attention which show extremely interesting pathologic changes in the lungs. A review of the literature shows considerable confusion in the classification of these changes. We feel that these cases belong to one relatively rare chronic lung disease which has been described under several names but up to now has been considered to be two separate entities.

One entity, historically called "muscular cirrhosis of lung," has been known since 1872 when it was described by von Buhl.7 Up to now, less than 30 cases have been reported in the world's literature under different names such as: "cirrhosis cystica pulmonum,"<sup>64</sup> "pulmonary muscular hyperplasia,"<sup>17,22,67,72</sup> "diffuse myomatosis and cyst formation,"66 "diffuse fibroleiomyomatosis hamartomatosis,"12 "bronchiolar emphysema,"8,47,59,74 "idiopathic diffuse bronchiolectasis,"20 "diffuse bilateral peribronchiolar and interstitial muscular hyperplasia associated with bronchiolar dilatation,"19 and "bronchiolar dilatation associated with muscular hyperplasia: polycystic lung."10

The other entity which appears identical to the one above was described in more recent time as the chronic form of "diffuse interstitial fibrosis of the lungs" known as Hamman-Rich syndrome. We found nothing of significance which would allow us to divide this one disease into two different entities and we found, too, that our 3 cases had all the characteristics needed for both.

Furthermore, we found 2 reports describ-

ing the chronic form of "diffuse interstitial fibrosis of the lungs" which mention the probability of these two being one and the same disease.<sup>14,44</sup>

#### REPORT OF CASES

Case I. A.L.N. was a moderately well nourished, well built 56 year old white male, a former Park Board employee, with a history of a progressive exertional dyspnea over several years and of frequent respiratory infections and chronic alcoholism.

The chest roentgenogram showed a typical "honeycomb lung" appearance in the lower fields and a persistent dense infiltrate in the middle lobe area (Fig. 1 and 2). A middle lobe lobectomy was performed.

The microscopic examination revealed epithelized cystic spaces with thickened walls. The



Fig. 1. Case 1. The chest roentgenogram prior to lobectomy of the middle lobe shows generalized fibrotic changes with a reticular pattern. There is also a "pneumonic" appearing heavier infiltrate in the right cardiophrenic area.

<sup>\*</sup> Staff Radiologist, Mir.neapolis Veterans Hospital, University of Minnesota Medical School.

<sup>†</sup> Staff Pathologist, Minneapolis Veterans Hospital, University of Minnesota Medical School.

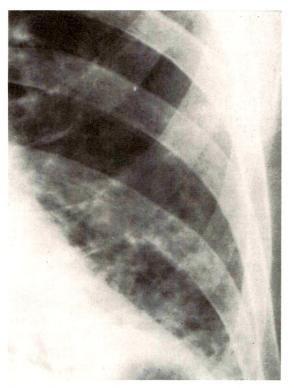


Fig. 2. Case I. A close-up view of the left lower lung in Figure I. Note the classic "honeycomb" appearance.

remaining alveoli contained many foreign body giant cells, mucinous material, and foamy macrophages. A microscopic diagnosis of "chronic interstitial pneumonitis" was made. The hemoglobin was 13.0 gm. per cent, the white blood cell count 15,000 per cubic mm. with slight increase in neutrophilic polymorphonuclears, and the blood pressure 125/75 mm. Hg. The electrocardiogram was suggestive of a right sided strain. Spirometric studies: vital capacity 1,400 ml.; I sec. forced expiratory volume 924 ml. (81 per cent of total); maximum breathing capacity 7,700 ml./min. (53 per cent of predicted value); total lung capacity 2,997 ml. (47 per cent of predicted value); residual volume 1,545 ml. and maximum mid expiratory flow 150 l./min.

At the time of his final admission, the patient developed a distal aortic and iliac arterial thrombosis, heart failure, and pneumonia which did not respond to therapy.

At autopsy, a classic "hobnail" appearance of the lungs was seen (Fig. 3) with multiple cystic dilatations measuring from a few millimeters to 1 cm. in diameter (Fig. 4). They were mostly

filled with mucoid material. The consistency was "fleshy" and the color tannish-brown. Microscopic examination revealed that the cystic dilatations were lined with respiratory type or with cuboid type epithelium and contained amorphous or mucoid material (Fig. 5). Some dilatations were lined with flattened epithelium, and, in several places, squamous metaplasia was seen. The thickened septa of the cystic spaces were composed of fibroconnective tissue where smooth muscle and elastic fibers were also seen. These spaces represent bronchiolectatic dilatations. In some areas, pronounced fibrosis of the alveolar septa was seen with focal areas of round cell infiltrates. In some places, accumulations of polymorphonuclears were present, indicating an acute pneumonic process. The heart showed right and left ventricular hypertrophy.

Case II. J.H.M. is a 49 year old well nourished and well built white male, a spray-painter. He had a history of a nonproductive cough for several years and an increasingly severe exertional dyspnea for the past couple of years. He was aware of clubbing of the fingers since childhood and stated that his father and brother also had similar clubbings; both died allegedly from

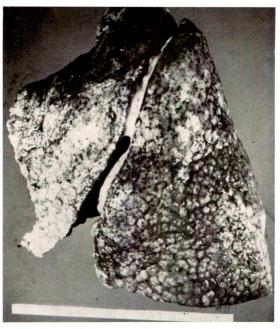


Fig. 3. Case I. The typical "hobnail" appearance of the lung is seen which quite closely resembles the liver afflicted with Laennec's cirrhosis. "Muscular cirrhosis of the lung."

liver diseases. The hemoglobin was 15.8 gm. per cent, and the white blood cell count 6,500 per cubic mm. with normal differential. Urine analysis, blood urea nitrogen and serum proteins were normal. The bromsulphalein test was 9.7 per cent, and the electrocardiogram was normal.

The chest roentgenogram revealed the presence of a reticulated fibrosis in both lower lungs and emphysematous bullae in the mid and upper lung fields (Fig. 6). The bronchogram showed only a mild but diffuse dilatation of the bronchial tree and some displacement of the bronchi due to emphysematous bullae (Fig. 7). The tuberculin (PPD) test gave a positive re-



Fig. 4. Case I. The cut section of the lung shown in Figure 3. Multiple cystic dilatations are seen which are most prominent "subpleurally." They are filled mostly with mucous material. The consistency is "fleshy."

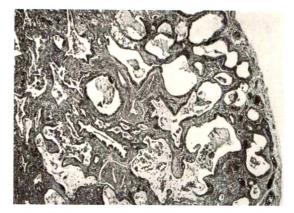


Fig. 5. Case I. A section of the lung shown in Figure 3, using low powered magnification. Multiple cystic dilatations of the nonrespiratory and respiratory bronchioles are seen. They are separated by connective tissue containing remnants from the collapsed alveoli.

action, but the sputa and bronchial washings were negative for acid fast bacilli, fungi, and neoplastic cells. The complement-fixation test for histoplasmosis, coccidioidomycosis and blastomycosis were negative. The pulmonary function tests indicated the presence of an alveolo-capillary block. Resting arterial pO<sub>2</sub> was 66.3 mm. Hg, and with exercise 50.5 mm. The alveolar-arterial pO<sub>2</sub> gradient was 46 mm. which also pointed to the existence of decreased diffusion capacity. Vital capacity was 2,100 ml. and the 1 sec. forced expiratory volume 1,500 ml. (71.5 per cent).

A biopsy specimen from the right middle lobe

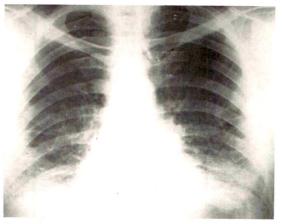


Fig. 6. Case II. The chest roentgenogram shows the generalized reticular type of fibrosis, most pronounced in the bases. Emphysematous bullae are noticeable in the mid and upper lung fields.



Fig. 7. Case II. The bronchographic appearance of the chest shown in Figure 6. A mild diffuse dilatation of the bronchial tree is noticeable. There is some displacement of the bronchi by emphysematous bullae. Note the absence of localized bronchiectasis and the nonfilling of the peripheral zone. The latter will be narrow in most advanced cases.

had a gross-nodular appearance and a poor compliance to pressure. The microscopic examination showed numerous cystic spaces, many lined with mucus-secreting columnar epithelium and others with cuboid epithelium. These cystic spaces were separated from each other by fibrous stroma containing smooth muscle (Fig. 8). The spaces were filled with mucinous material staining pale with eosin. Multinucleated cells and macrophages were seen in the spaces. The connective tissue of the walls was densely infiltrated with mononuclear cells and scattered polymorphonuclears with occasional eosinophils. This patient is being followed periodically on an outpatient basis and his disease seems to be stabilized for the time being.

Case III. This case is presented through the courtesy of the Pathology and Radiology Staffs of St. Luke's Hospital, Duluth, Minnesota, where this patient was last admitted and where the postmortem examination was carried out.

C.T. was a 70 year old white male with a good nutritional state and with a good body build. He was admitted to the hospital with a short history of dyspnea and chest discomfort due to congestive heart failure. There was no clubbing of the fingers. The hemoglobin was 15.7 gm.

per cent, the white blood cell count 16,000 per cubic mm. with 72 per cent polymorphonuclears, 25 per cent band forms, 15 per cent lymphocytes, 4 per cent eosinophils and 5 per cent metamyelocytes. The temperature was 97.2° F., radial pulse 124, and the blood pressure 140/80 mm. Hg. The electrocardiogram revealed a complete right bundle branch block, and occasional premature ventricular and atrial contractions. The blood urea nitrogen was 42.7 mg. per cent. Urinalysis showed a specific gravity of 1.021, pH 5.0 and was negative for sugar and albumin; in sediment 5 to 15 white blood cells, 5 to 10 red blood cells, 2 to 8 hyaline casts and few bacteria per high power field were present.

The chest roentgenogram demonstrated a far advanced widespread reticulated type of fibrosis (Fig. 9) with typical "honeycomb" type of radiolucencies in the lower lung fields (Fig. 10). The patient showed improvement at first but then expired quite suddenly. The main cause of death was considered to be cor pulmonale.

At autopsy, a classic "hobnail" appearance of the lungs was striking. Multiple cystic dilatations were present on cut section, being progressively larger in the periphery. Microscopically, the lung was composed of masses of fibrous, elastic and muscular tissues with a large number of irregular cystic cavities. These "cysts" were lined with ciliated respiratory epithelium, which produced a series of transitions into cuboid type with apparent loss of cilia and

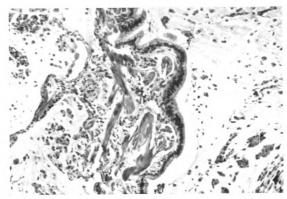


Fig. 8. Case II. A section from the middle lobe, biopsy specimen. Ciliated respiratory epithelium lines the dilated terminal bronchiole, which is filled with eosinophilic material and a few cellular elements. The characteristic abundance of the smooth muscle is seen in the walls of these bronchiolectatic dilatations.

with squamous metaplasia at places. These spaces represent dilated terminal and respiratory bronchioles. They contained mucus material and epithelial debris. Throughout the stroma, inflammatory infiltrates, composed mostly of lymphoctyes, plasma cells, histiocytes and polymorphonuclears were seen. The heart showed right and left sided hypertrophy.

#### DISCUSSION

Many articles are found in the literature about diffuse interstitial fibrosis of the lungs. 14,18,44,58,71 They describe a wide spectrum of different stages of activity, starting from the classic acute rapidly fatal forms (Hamman-Rich syndrome) through the subacute and chronic forms up to the advanced classic "honeycomb lung" with the presence of variable amount of smooth muscle hyperplasia (muscular cirrhosis of the lung). This latter may be scanty or strikingly abundant. 17,20,22,66,67,74

The acute form of this disease was described first in 1933 by Hamman and Rich<sup>25,26</sup> and is known to cause death within 6 weeks to 6 months. The first case where the known disease lasted longer than 6 months was reported by Potter and Gerber.<sup>58</sup> Now it can be stated that this disease follows more often a protracted course than the acute one.<sup>33</sup> A number of cases has been

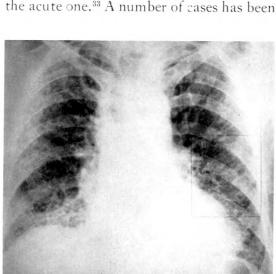


Fig. 9. Case III. This chest roentgenogram reveals an advanced, fully developed "honeycomb" type of fibrosis.



Fig. 10. Case III. The classic "honeycomb lung" appearance as seen in a close-up view of Figure 9.

reported which lasted over 10 years.<sup>44</sup> Over 100 cases including all stages have been described.

Donohue *et al.*<sup>14</sup> reported in 1959 that of 97 reviewed cases, 23 were familial. Of 31 familial cases,<sup>33</sup> 22 were females (71 per cent) and only 9 males (29 per cent). It is most probable that heredity occurs as a

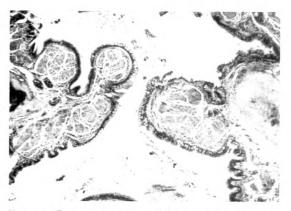


Fig. 11. Case III. Section of the lung shown roentgenographically in Figure 10. Markedly hyperplastic bundles of smooth muscle fibers are seen in the walls of the small bronchus which is identified by the presence of cartilage. There are many mucoid-producing cells in the respiratory epithelium.

dominant sex-linked trait. The acute form is well known with its rapidly developing dyspnea due to alveolo-capillary block, an aggravating nonproductive cough, and right sided heart and respiratory failure. There is usually fever, a slightly elevated white blood cell count and hypergammaglobulinemia.

Chronic forms have not been reported in children. This form represents a chronic progressive pulmonary disease with gradually increasing exertional dyspnea in an adequately nourished middle-aged person who gives no history of occupational hazards. There is classically a nonproductive cough. Much expectoration is always associated with secondary infection. Hemoptysis is sometimes seen. The white blood cell count is characteristically normal or slightly elevated with an almost normal differential count. Clubbing of the fingers occurs with secondary polycythemia,20 but Fraimow and Cathcart<sup>17</sup> were impressed by the fact that in their cases with clubbing there was no polycythemia. Clubbing without polycythemia occurred in our Case II. Pulmonary osteoarthropathy with typical periosteal cloaking also has been reported.44 Classically, there is only terminal pyrexia. Death is caused by cor pulmonale often aggravated by superimposed pneumonia (Cases I and III).

## **PHYSIOPATHOLOGY**

An alveolo-capillary block is found to be present by pulmonary function tests (Case II). 10,11,17,22 Alveolar gas-exchange is inhibited by the loss of many alveoli due to compression-obliteration by the disrupted capillary bed and by the altered epithelial lining in the cystic spaces. The physiologic dead space is increased (Case II). 17,22

# ROENTGENOGRAPHIC FINDINGS

In very early cases the chest roentgenogram may appear normal. Hughes<sup>38</sup> reports, however, that in 6 of 29 familial cases, the roentgenographic findings did precede the clinical symptoms. The very first roentgenographic appearance is a fine nodular infiltrate resembling "ground glass." This later takes a reticular pattern with fine radiolucencies, which finally, in the slowly progressive forms, turns into the typical "honeycomb lung." These changes are most prominent in the lung bases but may show wide distribution. In addition to it, various changes, common to most chronic lung disease, are seen, as well as superimposed acute and chronic pulmonic infiltrates (Fig. 1, 6 and 9).

Livingstone and associates<sup>44</sup> described the roentgenographic findings in 45 patients, most of whom had the slowly progressive form, although 10 were acute. They found the following distribution of infiltrates: lower lung—27, generalized or symmetrical—12, upper lung (mimics tuberculosis)—3, irregular—1, and uncertain—2. No pleural effusions occurred. Pneumothorax was quite common. Laminagrams were not especially helpful except for demonstration of the subpleural cystic dilatations.

Bronchography reveals a mild generalized dilatation of the bronchial tree without any localized bronchiectatic change. The findings are consistent with chronic bronchitis. Displacement of bronchi due to emphysematous bullae is seen (Fig. 7). The bronchographic illustrations shown by Christoforidis *et al.*<sup>10</sup> in their Case I and II reveal rather severe distortion of the bronchial tree; this was not seen in our cases. (These authors did not mention muscular hyperplasia in Case I and Case II was only suspected of having this disease.)

We obtained postmorten bronchograms of the lungs in our Case I by injecting barium sulfate into the bronchi. We must admit that the picture we obtained by forceful injection came closer in appearance to the cases of Christoforidis et al. (Fig. 14). In the less forcibly injected specimen (Fig. 13), the so-called "peripheral poolings" were seen. Some of these poolings corresponded to the centrilobular pooling in the studies of Leopold and Gough, 40 who identified these as dilated respiratory bronchioles (Fig. 12). The poolings which were located closer to the central pathway (Fig. 12 L)

would correspond to the dilated terminal bronchioles. 61 The appearance in Figure 14 is caused by the filling of the large subpleural cystic spaces, which cannot be filled during clinical bronchography (compare with Fig. 7). They represent dilated bronchioles.

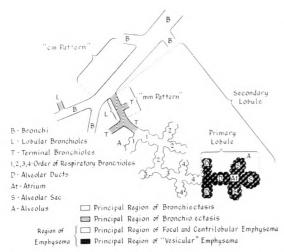


Fig. 12. The schematic outlay of the distal bronchial tree with the respiratory units. No clear-cut demarcation line is used to differentiate between the small bronchi (cartilage present) and proximal bronchioles (no cartilage)—both marked "B." Bronchioles, which contain alveoli in their walls, are called respiratory bronchioles. The last order of them divides into alveolar ducts, which are the last structures where muscle fibers are seen. The last bronchiole, where no alveoli are present, is called the terminal bronchiole. This, with all its divisional units, forms the acinus of the lung. Reid62 found that the last divisions which can be filled at bronchography represent the terminal bronchioles which branch off from a central pathway (Fig. 12 L). They are usually 2 to 3 mm. apart from each other and, for this reason, she calls this the "millimeter pattern" as opposed to the larger dividing bronchioles and bronchi which branch off 0.5 to 1 cm. apart—the "centimeter pattern." The dilatation of the bronchial tubes in the "centimeter pattern" level corresponds to bronchiectasis, while those occurring in the "millimeter pattern" represent bronchiolectasis, the category in which our entity belongs. Emphysema is defined as the dilatation of the respiratory bronchioles and their distal units;11,32 it may consist of dilatation alone or be accompanied by destruction of the walls of the alveoli or respiratory bronchioles. In this entity the cystic dilatations are located principally between the distal nonrespiratory and proximal respiratory bronchioles.

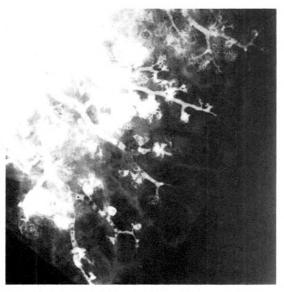


Fig. 13. Case I. The bronchial tree of the postmortem lung specimen is injected with barium sulfate suspension. The "peripheral poolings" are well demonstrated. (See text.)

We are inclined to believe that the socalled "flower pattern" ("peripheral pooling") in bronchography, <sup>16</sup> which is seen in association with asthma, <sup>35,36</sup> bronchitis, or emphysema <sup>15,75</sup> is a visualization of dilated respiratory bronchioles <sup>41</sup> and that the socalled "gullnut" appearance <sup>36</sup> represents dilated nonrespiratory bronchioles, the "preterminale Bronchiektase" of Loeschke. <sup>45</sup>

# DIFFERENTIAL DIAGNOSIS

The "honeycomb" appearance is seen in many lung diseases such as: xanthomatosis, biliary cirrhosis, tuberous sclerosis, <sup>56</sup> mesenchymomatosis, <sup>9</sup> thromboangiitis obliterans, <sup>34</sup> berylliosis, sarcoidosis, giant-cell pneumonia, scleroderma, tuberculosis after streptomycin therapy, pulmonary myomatosis and "adenomatosis. <sup>31,56</sup> Our entity includes only the diffuse bronchiolectatic "honeycomb lungs," where no etiologic factors or underlying disease can be found.

Often there is no way of differentiating an advanced form of diffuse interstitial fibrosis of the lungs from other "honeycomb lungs" without obtaining extrapulmonary roentgenograms, as in cases of sclero-derma, 55 tuberous sclerosis, rheumatoid

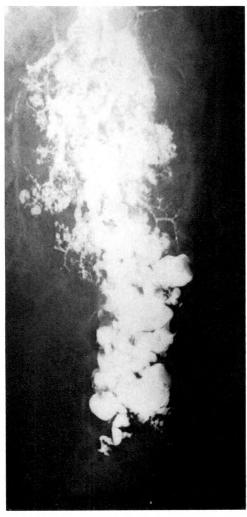


Fig. 14. Case I. A portion of the postmortem lung forcefully injected with barium sulfate suspension. The peripheral "subpleural" bronchiolectatic cystic dilatations are now filled, which does not occur during clinical bronchography. The distortion of distal nonrespiratory bronchioles, which may be seen at clinical bronchography in far advanced cases, is noted.

arthritis<sup>69</sup> and histiocytosis X. Sometimes, clinical history and laboratory findings are needed supplements to the roentgenographic findings, as in advanced "farmer's lung," disseminated lupus erythematosus, polyarteritis nodosa, and asbestosis. Other possibilities, such as idopathic hemosiderosis, viral pneumonias, etc., may have to be considered in certain cases. <sup>32,65</sup>

Sheft and Moskowitz<sup>72</sup> found among their 11 cases of "pulmonary muscular hy-

perplasia" 5 which showed hilar or mediastinal lymphadenopathy (5 of the 11 cases reported previously).<sup>17</sup>

These authors feel that such lymph node enlargement is an important clue for diagnosis. This, however, may point only toward some other associated disease. Of the 5 patients with lymphadenopathy in the thorax, I who had mediastinal widening showed the presence of alveolar carcinoma and another with bilateral hilar lymphadenopathy showed cells with malignant changes in bronchial aspirate. The third case with enlarged paratracheal lymph nodes showed changes at cervical biopsy which were consistent with sarcoidosis (no granulomatous process, however, was found in the biopsy specimen of the lung).

## PATHOLOGY

Early, there is edema in the alveolar septa and a serofibrinous exudate in alveoli. Next, a mononuclear infiltrate is seen in the alveolar walls principally with pulmonary macrophages and histiocytes. Clusters of these are also seen in alveolar spaces. An eosinophilic fibrinous hyaline membrane is present contiguous to the inside of the alveolar wall. Macroscopically, the lung is red and has a firm consistency.<sup>44,68</sup>

Later, the alveolar septa show a marked thickening due to proliferation of fibroblasts and the presence of lymphocytes, plasma cells, and monocytes. The alveoli are lined with cuboid cells. The capillaries are first dilated but later collapse. The next phase reveals a decrease in the cellular infiltrate. The marked thickness of the alveolar walls is caused by connective tissue proliferation, mainly reticulin substance. <sup>29,60,71</sup>

If the patient survives this phase, then the final "honeycomb lung" develops. This is characterized by the deposition of collagen which undergoes hyalinization. The alveoli are now collapsed and replaced by dense, hyalinized connective tissue. The capillaries are absent. Pulmonary-bronchial arterial anastomoses open up or develop. The respiratory and terminal bronchioles dilate cystically and almost reach the pleu-

ral surface and septa, being separated from these only by fibrotic tissue which contains the remnants of the collapsed fibrosed alveoli. These cystic spaces are mostly lined by ciliated respiratory epithelium (Fig. 5 and 8) where mucus-producing cells are seen also; these represent the terminal and the "lobular" bronchioles (Fig. 12). For this reason the term "diffuse bronchiolectasis" is considered more proper<sup>20</sup> than "bronchiolar emphysema." Some cystic spaces are lined with cuboidal or flattened epithelium and, while not having the mucus-producing cells, they represent the dilated respiratory bronchioles. Squamous metaplasia is often seen.

The presence of smooth muscle hyperplasia is considered classical for "muscular cirrhosis of the lung" but variable in amount, 18,88,50,68,70 and sometimes hard to find.20 It is seen interstitially as well as peribronchially (Fig. 8 and 11). One should keep in mind that the presence of smooth muscle proliferation is not a pathognomonic finding. It is seen in many chronic pulmonary diseases such as chronic pneumonia, syphilis,66,78 bronchiectasis, emphysema, abscess, bronchiolitis, tuberculosis, and tumors.48 A striking muscular hyperplasia has been reported also in pulmonary lymphangiectasia<sup>84</sup> and in chylothorax.<sup>5,88</sup> These latter conditions may also have a "honeycomb" appearance. The same can be said for the pronounced muscular hyperplasia in tuberous sclerosis.8,4

Macroscopically, the typical "hobnail" lung (Fig. 3) is seen in "muscular cirrhosis of the lung" as well as in cases reported as chronic Hamman-Rich syndrome. 83,50,68,78 This appearance is caused by subpleural bulgings of numerous cystic dilatations, many of which contain mucous material. In addition, the color of the lung is brownish yellow, which makes one feel that the historic purely descriptive term "cirrhosis" (kirros=orange yellow) is not out of place. The cut surface (Fig. 4 and 5) reveals the presence of numerous cystic spaces communicating with the bronchial tree. Their diameters range from a few millimeters to

I cm. and occasionally more. The consistency is fleshy-firm.

When we compared our 3 cases with those reported under the category "muscular cirrhosis of the lung" and with the advanced stage of the chronic diffuse interstitial pulmonary fibrosis, we came to the conclusion that these conditions are one and the same disease. We found that the roentgenologic, clinical, pathophysiologic, and macro- and micropathologic aspects matched each other completely. We found that this thought has been expressed previously by Donohue et al.14 and by Livingstone et al.44 Further support for our conviction, that these two conditions represent the same disease is found in the report by Hughes.88 He describes 3 cases of diffuse interstitial pulmonary fibrosis in one family, all adults. Two daughters developed the classic acute Hamman-Rich syndrome which was proven by lung biopsies. Both cases responded favorably to steroids and remained in remission at the time of Hughes' report. The 70 year old mother died from a chronic form of the diffuse interstitial fibrosis of the lungs in spite of steroid therapy. Classic "hobnail" lungs were seen at autopsy and the microscopic findings seemed identical to those described under "muscular cirrhosis of the lung" category. The ultimate proof for the conclusion that the so-called 'muscular cirrhosis of the lung" is the same as the advanced form of the chronic diffuse interstitial fibrosis of the lungs (Hamman-Rich syndrome) would require serial biopsies on patients who are inflicted with but survive the more acute forms of Hamman-Rich syndrome.

The etiology of this disease has not been established. Siebert and Fisher<sup>74</sup> postulate the presence of a congenital hypoplasia in the distal respiratory units. Heppleston<sup>31</sup> does not believe that the discussed entity really represents a separate disease and classifies it just as another "fibrocystic lung." He believes that the main etiologic factor is an underlying obstructive bronchiolar infection or granulomatous process. However realistic this theory appears for

many "honeycomb lungs," we believe that it does not apply to the entity under discussion. The latter has an insidious progressive course with nonproductive cough and dyspnea; sometimes clubbing of the fingers occurs before these symptoms are evident.

This condition closely resembles "collagen diseases." From the chest roentgenographic appearance alone (when no diagnostic roentgenograms from the joints are present), one may not be able to distinguish it from lung changes in rheumatoid arthritis, though serologic tests may be helpful. The presence of lupus erythematosus cells and involvement of kidneys makes possible the differentiation of lupus erythematosus. Scleroderma has its typical extrapulmonary roentgenologic and clinical findings. 55 An alveolo-capillary block is common in all of

Rubin and Lubliner<sup>68</sup> postulate an autoimmune mechanism or a delayed sensitivity to an unrecognized microorganism as an etiologic factor. Another similarity with many collagen diseases is its favorable response to the corticosteroids. Rare spontaneous remissions have been reported.44 The genetic factors, as mentioned previously, play a significant role in about 24 per cent of cases.14

A more detailed description of our 3 cases will be reported elsewhere. The categories "muscular cirrhosis of the lung" and the chronic form of "Hamman-Rich syndrome" will be discussed more extensively with emphasis on pathogenesis.

## SUMMARY

The literature on the rare lung disease, historically called "muscular cirrhosis of the lung" ("bronchiolar emphysema") and in this article "diffuse bronchiolectasis with muscular hyperplasia" as the preferred name, was reviewed and 3 new proven cases are reported. The literature on the acute and chronic forms of Hamman-Rich syndrome (diffuse interstitial fibrosis of the lungs) was also reviewed and all findings compared to each other and to our 3 new cases. We conclude that "diffuse bronchiolectasis with muscular hyperplasia" ("muscular cirrhosis of the lung") represents, in all likelihood, the advanced stage of the chronic form of the Hamman-Rich syndrome with variable amounts of smooth muscle hyperplasia.

All the roentgenologic, clinical, laboratory, pathophysiologic, gross and micropathologic aspects were found essentially the same in both diseases.

The diagnosis, the roentgenologic differential diagnosis and the similarity with "collagen disease" are discussed.

H. Kuisk, M.D., D.Sc. Department of Radiology Minneapolis Veterans Hospital 54 Street and 48 Avenue, South Minneapolis, Minnesota 55417

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# ANGIOCARDIOGRAPHY IN DIAGNOSIS OF AGENESIS OF A LUNG\*

By ISRAEL STEINBERG, M.D.,† and HARRY L. STEIN, M.D.‡

THE definitive diagnosis of early during absence (agenesis) of a lung during THE definitive diagnosis of congenital life can be made by angiocardiography. This became evident in 1939 with the publication of the method of angiocardiography by Robb and Steinberg.<sup>22</sup> The value of contrast visualization of the pulmonary circulation and cardiovascular structures in severe pulmonary fibrosis (fibrothorax) of the right lung due to bronchiectasis (which simulates pulmonary agenesis) was described in a separate article in the same year.28 In a review of the method in 1940,23 the value of angiocardiography in massive left pulmonary fibrosis (fibrothorax) following pulmonary tuberculosis, a condition which also resembles absence of a lung, was reported. Subsequently, Castellanos and Pereiras,3 in 1942, Ingram, Hudson, and Davis,12 in 1950, Wexels,39 and Fouquet and co-workers,8 in 1951, Lukas, Dotter, and Steinberg,14 and Rev and Rubinstein,21 in 1953, de Cordova,5 in 1954, Clark et al.,4 and Bariety and colleagues,1 in 1955, and Turiaf and co-workers,36 in 1962, reported angiocardiographic studies of patients with pulmonary agenesis. Smith and Bech,<sup>26</sup> in 1958, even though they found homogeneously dense left lungs in antemortem roentgenograms of 3 of their 4 cases, stated that the diagnosis of agenesis of a lung based on conventional roentgenography, bronchoscopy, and bronchography was only presumptive and offered no more than a strong suspicion of the existence of agenesis.

In the present report, the value of angiocardiography in a diagnosis of agenesis of a lung in 2 new cases is demonstrated. A 13 year follow-up report of another patient with agenesis of the left lung and a patent ductus arteriosus with reversal of blood flow, previously published, is also included. Two other patients with anomalous nonconstricting left pulmonary arteries to a lung devoid of a left upper lobe are contrasted with those with complete absence of a lung. Finally, illustrative examples of pulmonary disease that may simulate pulmonary agenesis and need to be differentiated from congenital absence of a lung are described and discussed.

#### REPORT OF CASES

CASE I. Agenesis of the right lung and left superior vena cava. A 9 month old Negro female was referred for angiocardiography by Dr. Henry P. Goldberg. She was born at term, weighed 6 pounds, 14 ounces at birth and was well when discharged from a hospital in a nearby city. She returned to the same hospital after 3 weeks because of a respiratory infection. A roentgenogram of the chest demonstrated a dense right hemithorax and agenesis of the lung was suspected. The weight on discharge after the second admission was only 6 pounds, 12 ounces. Subsequently, she was readmitted 3 more times because of respiratory infections and then transferred to The New York Hospital on January 2, 1965, for angiocardiography.

Physical examination disclosed a well-developed but poorly nourished infant, weighing 5.6 kg. and measuring 64 cm. in length (12 pounds, 6 ounces and 21 inches). The chest was symmetric but dullness and diminished breath sounds were heard over the right hemithorax; on the left side, the lung was resonant and the breath sounds were clear. There were no rales and the infant was afebrile. The heart was felt in the right fourth interspace in the mid-axillary line;

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‡ Whitehall Fellow in Cardiovascular Radiology.

the rate was regular, 140 per minute. The heart sounds were heard over the right hemithorax, front and back. A loud, harsh (Grade 2-4) systolic murmur was heard at the base of the heart. The electrocardiogram showed abnormal position of the heart in the right hemithorax. The roentgenograms of the chest demonstrated a dense right hemithorax (Fig. 1, A and B). Simultaneous biplane angiocardiograms in frontal and lateral views disclosed marked dextrorotation of the cardiovascular structures in a clockwise direction<sup>31</sup> (Fig. 1, C, D, E and F). Late in the series, venous return of contrast material visualized a left superior vena cava entering the coronary sinus. The infant was discharged and so far has been free of respiratory complaints.

Case II. Agenesis of the left lung in an asymptomatic 41 year old Caucasian man. This patient was well and served in the army as an infantryman from 1936 to 1939. He was then recommended for a commission but physical and roentgen examinations showed a "collapsed lung" and he was discharged from the service. In 1962, from pre-employment roentgenograms of the chest, agenesis of a lung was suspected and he was referred to The New York Hospital for angiocardiography. He weighed 150 pounds and was 5 feet,  $7\frac{1}{2}$  inches tall. The thorax was symmetric, the left hemithorax was dull and the breath sounds over this side were absent. The right hemithorax was resonant and the breath

sounds were clear; no rales were heard. The heart was regular and the blood pressure was normal, 140/70 mm. Hg.

Conventional roentgenograms of the chest demonstrated a high left diaphragm and a dense small left hemithorax with marked deviation of the trachea, mediastinum, and right lung into it (Fig. 2, A and B). Angiocardiograms on February 2, 1962, showed rotation of the heart and cardiovascular structures into the right hemithorax in a counterclockwise direction, assuming the position of a right oblique view; the pulmonary artery appeared dilated (Fig. 2C).

CASE III. Thirteen year follow-up report of agenesis of the left lung and patent ductus arteriosus with reversal of blood flow (Fig. 3, A, B, C and D). This patient, now a 35 year old man and still living, was previously reported in 1953.14 At that time, ligation of the ductus was not advised because of severe pulmonary hypertension, 113/70, mean 72, compared to the systemic pressure (femoral artery) of 117/70, mean 70 mm. Hg. He was discharged from The New York Hospital on March 22, 1952, and returned to Iran where he limited his activities but became increasingly more dyspneic. A year prior to readmission (on September 6, 1962), he began having fainting spells, weight loss, epistaxis, and bleeding from the gums.

Physical examination showed a poorly nourished male with rubor of the face, upper thorax,

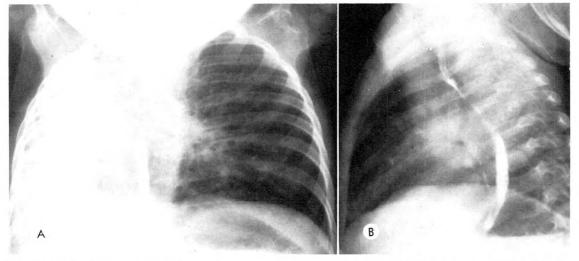


Fig. 1. Case I. (A) Frontal esophagram showing a homogeneously dense right hemithorax. Notice that the left pulmonary artery originates in the right hemithorax. (B) Lateral roentgenogram showing posterior displacement of the esophagus and aeration of the retrosternal space.

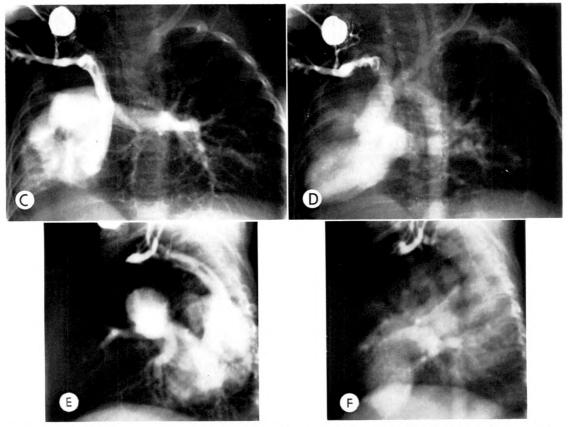


Fig. 1. (C) Frontal angiocardiogram demonstrating the marked dextrorotation of the superior vena cava, right atrium and ventricle, and pulmonary artery. Note the solitary elongated left pulmonary artery with widely separated branches supplying the left lung which also occupies a portion of the right hemithorax. (D) Later in the series, the left atrium, ventricle, and aorta are opacified. Note the extreme dextrorotation of the left cardiac chambers and aorta; indeed, the left ventricle is in ventral position, and the right ventricle is dorsal. (E) Simultaneous, biplane, lateral angiocardiogram of C showing the posterior dislocation of the superior vena cava, right cardiac and pulmonary arterial systems. (F) Simultaneous, biplane, lateral angiocardiogram of D demonstrating the anterior position of the left cardiac chambers and aorta.

and fingers (Fig. 3E). There was mild clubbing of the hands and more severe clubbing and cyanosis of the toes (Fig. 3F). The left hemithorax was flattened and dull, and the breath sounds were absent at the base. The heart was regular, there was a precordial heave and a systolic thrill was palpable in the left midaxillary line. The pulmonic second sound was split. The blood pressure was 125/90 mm. Hg. The electrocardiogram showed right ventricular hypertrophy. The venous pressure was 140 mm. water. Blood studies showed an erythrocyte count of 12 million per cubic mm., hemoglobin 23.8 gm./100 ml., and hematocrit 83 per cent. On discharge in 1952 the erythrocytes were 7.7 million per cubic mm., hemoglobin 21.7 gm./100 ml., and hematocrit 70 per cent. A chest roentgenogram made on readmission to The New York Hospital on September 7, 1962, showed the left hemithorax to be smaller than the opposite side. The right lung was overdistended and stretched into the upper portion of the left hemithorax while the trachea and mediastinum were more deviated into the left hemithorax (Fig. 3G). Again, ligation of the ductus was not advised because of worsening of the polycythemia, pulmonary hypertension, and reversed blood flow through the ductus. After a series of phlebotomies, the hematocrit was reduced to 72 per cent and he was discharged. Recent correspondence, through the courtesy of Dr. Claude E. Forkner, disclosed

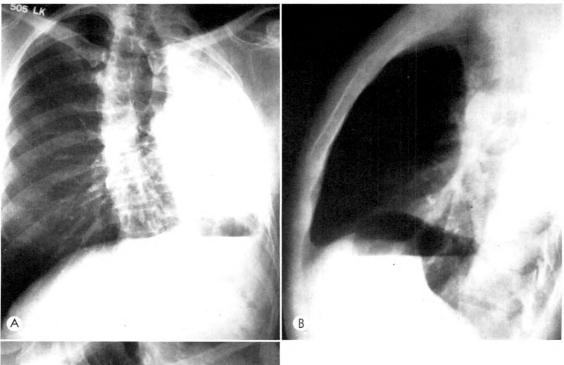




Fig. 2. Case II. (A) Frontal teleroentgenogram' of the chest showing a dense left hemithorax, elevated left diaphragm, and marked tracheal and mediastinal herniation into the small left hemithorax. (B) Lateral roentgenogram of the chest demonstrates hyperlucency of the anterior portion of the thorax. (C) Frontal angiocardiogram revealing marked displacement of the superior vena cava, right cardiac chambers, and pulmonary artery into the left hemithorax, assuming the position of the right oblique view. Note the solitary right pulmonary artery which is dilated to supply the right lung which also extends into the summit of the left hemithorax above the cardiac structures.

that though severely handicapped by dyspnea on slight to moderate exertion, he was still alive.

## DISCUSSION

Agenesis of a lung has long been considered a rare condition, and yet, at the rate new cases are being reported, it may

soon become an uncommon rather than a rare disease. Indeed, almost every roent-genologist has encountered a case and the files of many of the larger hospitals contain 1 to 3 cases. In 1955, Valle<sup>37</sup> in reporting a case tabulated 120 from the world's literature. Before him, Hurwitz and Stephens,<sup>11</sup>

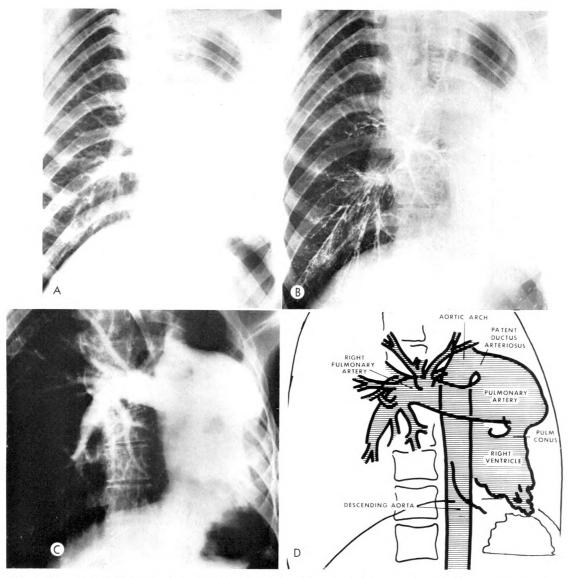


Fig. 3. Case III. (A) Frontal teleroentgenogram of the chest, made in 1952, showing the dense lower two-thirds of the left hemithorax, elevation of the diaphragm, herniation of the trachea and mediastinum into the left hemithorax, and an overdistended right lung which reaches the upper third of the left hemithorax. (B) Bronchogram, made in 1952, demonstrates only a single right bronchus; the left is absent. (C) Frontal angiocardiogram, also made in 1952, shows the marked deviation of the right heart chambers and pulmonary artery into the left hemithorax. The descending aorta is opacified directly from the pulmonary artery, establishing the diagnosis of reversal of the shunt. Note the plethoric solitary right pulmonary artery whose branches reach into the upper third of the left hemithorax. (D) Tracing of C. (A-D reproduced by permission from The New England J. Med. 14)

Deweese and Howard,<sup>6</sup> Smart,<sup>25</sup> Wexels,<sup>39</sup> and Oyamada *et al.*<sup>20</sup> reviewed the literature and separated the cases of complete agenesis of a lung from the partial (lobar hypoplastic) types. Smith and Bech<sup>26</sup> in 1958 added 4 autopsy proven cases of

complete agenesis of a lung and brought the literature up to date. Additional cases of complete agenesis of a lung reported in the literature since then bring the total number of cases to about 160.<sup>2,9,10,13,19,24</sup>, <sup>33,40</sup> There appears to be no sex predilec-

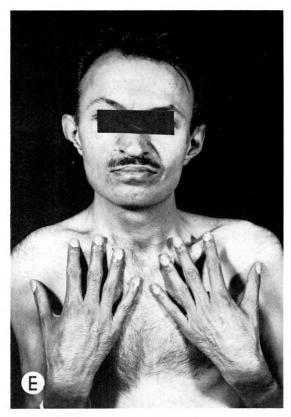


Fig. 3. (E) Photograph, made in 1962, showing rubor of the face, upper thorax, and hands.





Fig. 3. (G) Conventional teleroentgenogram of the chest made in 1962, 10 years after A, showing some increased overdistention of the right hemithorax with further retraction of the left hemithorax.

tion; left-sided agenesis occurs more often than right.<sup>37</sup>

The embryonic development of pulmonary agenesis, though unknown, is believed to be due to inherent faulty germ plasm resulting in development of defective respiratory, pulmonary, and pulmonary vascular structures. An error of genetic origin also seems probable because of the frequent association of other congenital abnormalities. The influence of a teratogenic factor was demonstrated in the experiments of Wilson and Warkany, Markany, Markan

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Fig. 3. (F) Photograph of lower extremities and hands, made in 1962, revealing the contrast between the deep cyanosis of the feet and clubbing of the toes and rubor and mild clubbing of the hands.

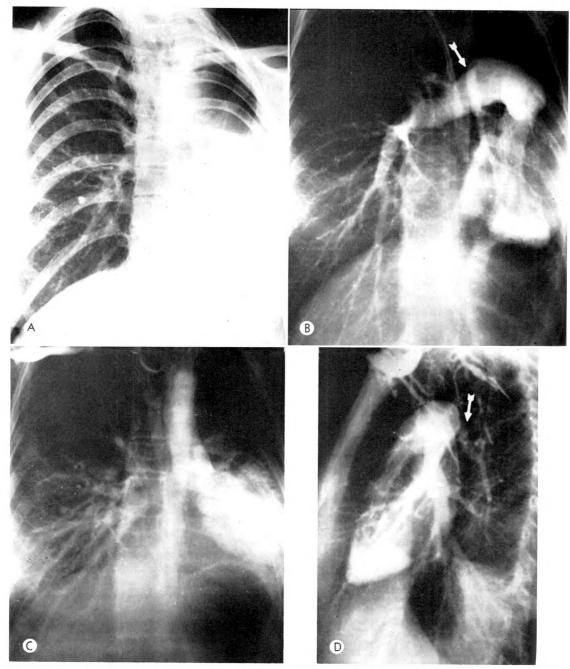


Fig. 4. Congenital absence of the left upper lobe in a 17 year old girl with congenital left facial paralysis and absent left kidney. (A) Frontal teleroentgenogram of the chest showing the dense left lower two-thirds of the left hemithorax, elevation of the left hemidiaphragm, and herniation of the trachea and mediastinum into the left hemithorax. Note that the upper third of the left hemithorax is lucent. (B) Frontal angiocardiogram showing rotation of the superior vena cava, right cardiac chambers, and pulmonary artery into the left hemithorax. The left pulmonary artery (arrow) has an anomalous course, is hypoplastic, and supplies the left lower lobe. The left upper lobe is absent (there was also an absent left upper lobe bronchus). (C) Frontal angiocardiogram, later in the series, shows the pulmonary veins of the right lung markedly contrasting with the tiny pulmonary veins from the anomalous left lower lobe. (D) Lateral angiocardiogram showing the anomalous nonconstricting left pulmonary artery (arrow) descending posteriorly. (Courtesy of Dr. Edgar E. Mannix. 16)

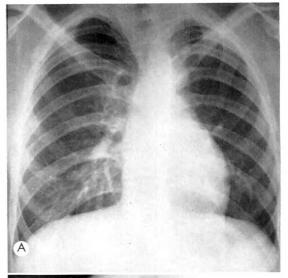
A deficiency. Despite absence of a lung and the pulmonary artery, asymmetry of the thorax, except for flattening of the affected side, is uncommon on physical examination. It would appear, therefore, that the formation of the chest wall in fetal life is independent of normal lung growth.

Clinically, in addition to some flattening of the affected hemithorax, the trachea, mediastinum, and heart are usually deviated towards the side of the absent lung. When the right lung is absent, the heart is on the same side (Fig. 1, C; D; E; and F) and is often mistaken for dextrocardia. The breath sounds may be absent over the affected side, which is also dull to percussion. The opposite lung may be resonant and often there may be normal breath sounds at the summit of the affected lung due to the overdistention and herniation of the good lung. The conventional roentgenogram of the chest shows the affected side to be dense and homogeneous, the diaphragm is elevated, and the trachea and opposite lung are herniated into the affected hemithorax (Fig. 1A; 2A; 3A; and 3G). The heart is obscured in the dense hemithorax while a normal pattern of pulmonary vasculature is present in the unaffected hemithorax. Roentgenoscopy may show limited respiratory excursions on the affected side. Bronchography may be of diagnostic aid by demonstrating absence of a bronchus (Fig. 3B).

Angiocardiography, by showing complete absence of pulmonary and bronchial arteries and lung, provides information formerly obtainable only at autopsy. Rota-

tion of the heart into the side of the absent lung can also be clearly visualized (Fig. 1, A–D; 2C; and 3, C and D). Associated cardiac anomalies, a left superior vena cava as in Case 1 and reversal of shunt of a patent ductus arteriosus (Fig. 3, C and D) may also be demonstrated.

The differential diagnosis of agenesis of a lung includes partial or lobar agenesis of a lung. Figure 4, A-D shows that the conventional roentgenogram of absence of the left upper lobe (Fig. 4A) may be indistinguishable from one showing complete



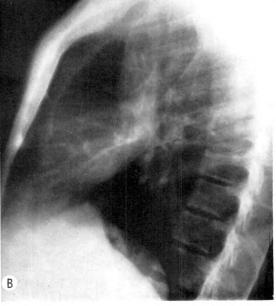


Fig. 5. Anomalous (nonconstricting) left pulmonary artery in a 15 year old boy with absence of the left upper lobe and congenital thoracic hemivertebra. (A) Frontal teleroentgenogram of the chest showing scoliosis of the thoracic spine and marked diminution of the left lung vasculature. (B) Lateral teleroentgenogram of the chest showing anterior bulging of the sternum and overdistention of the lungs.

agenesis of a lung. Yet, bronchograms and angiocardiograms (Fig. 4, B, C and D) clearly demonstrate that a left lower lobe is present and occupies the entire left hemithorax. Rotation of the heart structures into the left hemithorax in the right anterior oblique position was pronounced. Another patient recently reported (Fig. 5, A-E)<sup>32</sup> with an identical lesion, an anomalous left pulmonary artery which also supplied the left lower lobe, the upper being

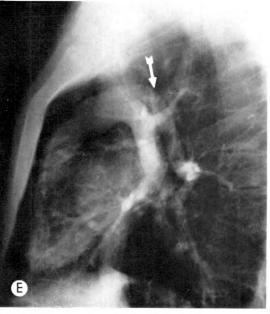
absent, differed markedly from the above case in that there was neither rotation of the heart nor mediastinal herniation into the left hemithorax. Still another patient with marked density of the right lung, tracheal deviation, and herniation of the left lung into the right hemithorax (Fig. 6A) was found to have dextrorotation of the heart and aplasia of the right lower lobe (Fig. 6B).

A case of congenital absence of a right



Fig. 5. (C) Bronchogram demonstrating absence of the left upper lobe. (D) Frontal angiocardiogram showing that the left pulmonary artery is hypoplastic and has an unusual origin and course (arrow). (E) Lateral angiocardiogram showing that the small left pulmonary artery courses posteriorly into the left hemithorax (arrow). (A–E reproduced by permission from Circulation.<sup>32</sup>)





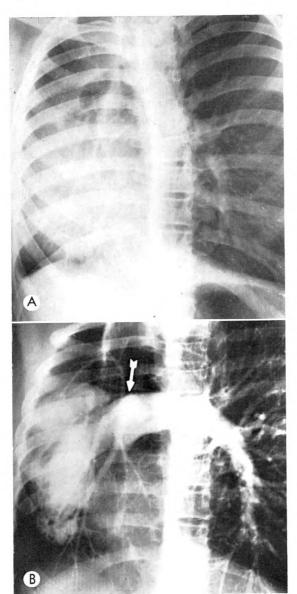


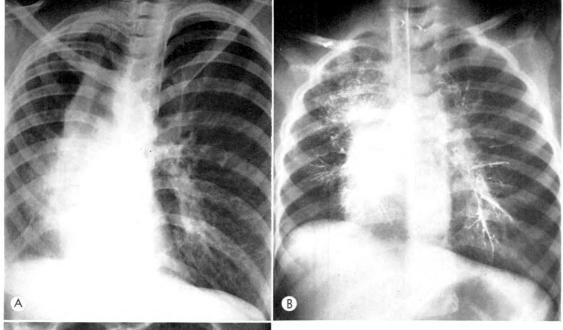
FIG. 6. Destrorotation of the heart and hypoplasia of the pulmonary artery in a 14 year old girl who complained of dyspnea. (A) Frontal teleroentgenogram showing a partially obscured right hemithorax due to displacement of the cardiovascular structures. There is herniation of the trachea and mediastinum toward the right hemithorax. (B) Frontal angiocardiogram showing dextrorotation of the heart with spreading of the left pulmonary artery branches, a hypoplastic right pulmonary artery, and absence of the right lower lobe (arrow).

pulmonary artery, because of tracheal deviation and mediastinal herniation, at first glance appeared to be similar to agenesis of a lung (Fig. 7A). However, bronchograms

showed that the right lung was present (Fig. 7B). Angiocardiograms demonstrated that the right pulmonary artery was absent and that the small right lung recieved nutrient vessels from the bronchial arteries (Fig. 7C).<sup>31</sup>

Advanced bronchiectasis of either lung when it is accompanied by severe pulmonary fibrosis may cause pronounced deviation of the mediastinal structures to the affected side, accompanied by hypoplastic pulmonary arteries, and simulate pulmonary agenesis. Such was the situation in a patient with right-sided bronchiectasis (Fig. 8, A and B). However, the bronchogram (Fig. 8B) by demonstrating bronchiectasis and the angiocardiogram by showing a small hypoplastic right pulmonary artery ruled out pulmonary agenesis (Fig. 8C). Fibrothorax due to tuberculosis. especially after pneumothorax, thoracoplasty, or pneumonectomy, may simulate congenital pulmonary agenesis (Fig. 9A).17, <sup>29,30</sup> Angiocardiograms by demonstrating a hypoplastic, albeit intact, pulmonary artery (Fig. 9B) establish the presence of a lung.

Finally, bronchogenic carcinoma may cause complete atelectasis of a lung and produce the homogeneous density, tracheal deviation and herniation of the opposite lung. Angiocardiography in such a patient revealed an intact right pulmonary artery with distorted and compressed peripheral branches (Fig. 104). The history, physical signs, and positive cellular or tissue biopsy, however, readily established the diagnosis of cancer. In the early phase following pneumonectomy for lung cancer, the pleural cavity contains fluid and, before organization of the space, the heart and mediastinal structures remain unaltered (Fig. 10B). In such a case, the stump of the pulmonary artery can be visualized, thus establishing that the absence of the lung was due to pneumonectomy. In another patient who developed the superior vena cava syndrome 3 years after a right pneumonectomy, the characteristic rotation of the trachea and heart into the oper-



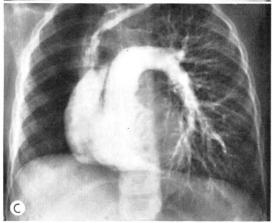
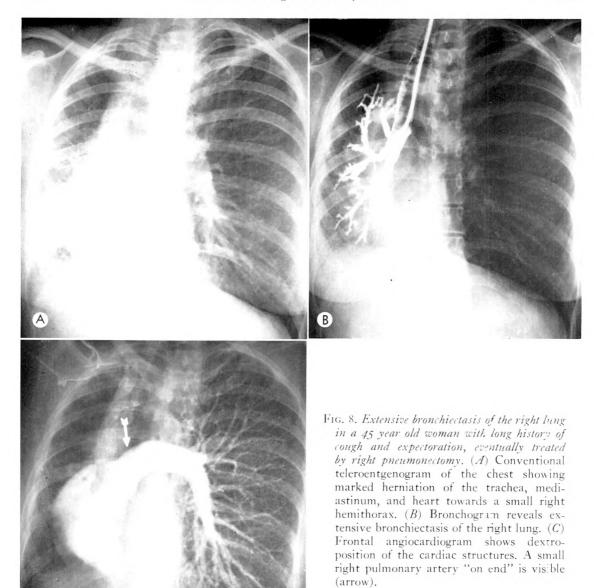


Fig. 7. Congenital absence of the right pulmonary artery in a 6 year old boy who had recurrent upper respiratory infections. (A) Frontal teleroentgenogram of the chest showing aeration of a small hypovascular right lung. There is marked tracheal, mediastinal and cardiac herniation towards the right hemithorax. (B) Frontal bronchogram demonstrating that the right bronchus and branches are present and intact. (C) Frontal angiocardiogram showing congenital absence of the right pulmonary artery. The small right lung receives nutrient vessels from the bronchial arteries.

ated hemithorax as well as the lung herniation was evident (Fig. 10C). Of interest was the superior vena cava involvement by recurrent cancer. In contrast is the marked left fibrothorax of a 9 year old child who had had a pneumonectomy 3 years earlier for bronchiectasis (Fig. 10D). Differentiation from congenital agenesis of the left lung was made by observing that the left thoracic cage contained metallic sutures in the ribs, evidence of a left pneumonectomy.

It appears that when congenital absence of a lung is uncomplicated by congenital anomalies, long life may follow. Valle<sup>37</sup> cited a woman of 72 years with an absent

left lung who died of unrelated causes. One of our patients with agenesis of the left lung is alive and well at the age of 45 years (Case II). On the other hand, the man with left lung agenesis and a patent ductus arteriosus with reversal of blood flow (Case III) is seriously disabled by anoxia, polycythemia, and pulmonary arteriosclerosis. 14,15 Although the patient is now 35 years old and has had reversal of blood flow through the ductus for many years, pulmonary arterial calcification was not recognized. 33 It may be, however, that the fibrothorax makes recognition of pulmonary arterial calcification difficult (Fig. 3G). Valle 37 and



others<sup>25,26</sup> have also pointed out that patients with right-sided pulmonary agenesis die at an earlier age than those with left-sided disease. Case I, described above, suffered repeated respiratory infections and was below the average weight and physique of infants in her age group. Another hazard, irrespective of the side affected, is

aspiration of foreign bodies with resultant pneumonia in the only lung, with catastrophic results. 10,18.35

Schneider's<sup>27</sup> classification of pulmonary agenesis has been used for years. His Class I referred to true aplasia (or agenesis) when the lung and its pulmonary artery were absent. In Class II the lung and artery

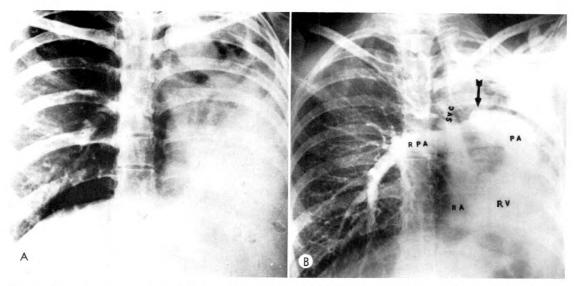


Fig. 9. Extensive active pulmonary tuberculosis causing left fibrothorax in a 30 year old woman. (A) Frontal teleroentgenogram showing a dense left lung obscuring the heart. The trachea and mediastinum are also herniated into the left hemithorax. Note the left infraclavicular cavities. (B) Frontal angiocardiogram revealing the dislocation of the superior vena cava (SVC), right atrium (RA), right ventricle (RV), and pulmonary artery (PA) into the left hemithorax. The right pulmonary artery (RPA) originates in the left hemithorax; the left pulmonary artery is small and is seen "on end" (arrow). (Reproduced by permission from the J.A.M.A.<sup>23</sup>)

were absent, but a rudimentary bronchus came off the trachea; while Class III consisted of cases of a hypoplastic lung which had a fully formed but reduced in size bronchus which ended in a fleshy structure without lobes. These categories have proved valuable for postmortem and bronchographic classification.25,37 In the living, considerable additional data regarding the pulmonary vasculature of the affected and opposite lung, the cardiac chambers, and associated cardiovascular anomalies, if present, can be secured by angiocardiography. By itself, angiocardiography can be expected to establish the diagnosis of pulmonary agenesis (Fig. 1, C-F; 2C; and 3C). Angiocardiography combined with bronchography is capable of providing very significant data for the diagnosis of lobar agenesis (Fig. 4, A-D; and 5, A-E). By showing persistent remnants of the pulmonary circulation, angiocardiography is also of benefit in differentiating acquired (infections, traumatic, and neoplastic) pulmonary disease from pulmonary agenesis (Fig. 8-10, inclusive).

#### SUMMARY AND CONCLUSIONS

In 2 cases of complete agenesis of a lung, angiocardiography permitted the definitive diagnosis by demonstrating absent pulmonary and bronchial arteries and lung. In Case I, an infant of 9 months with agenesis of the right lung, there was severe dextrorotation of the great vessels and cardiac chambers into the right hemithorax. The infant had recurrent respiratory infections and was underweight. Case II, an adult of 41 years, demonstrated absence of the left lung and was asymptomatic. His cardiovascular structures were rotated into the left hemithorax and assumed the right oblique position. The remaining pulmonary artery was dilated and distended. The contrast between these 2 patients and Case III, with agenesis of the left lung and reversal of blood flow through a patent ductus arteriosus, was striking. The latter patient, after a follow-up period of 13 years, was severely disabled by anoxia, polycythemia, and pulmonary hypertension (arteriosclerosis). It would appear, therefore, that the prognosis of patients with agenesis of a

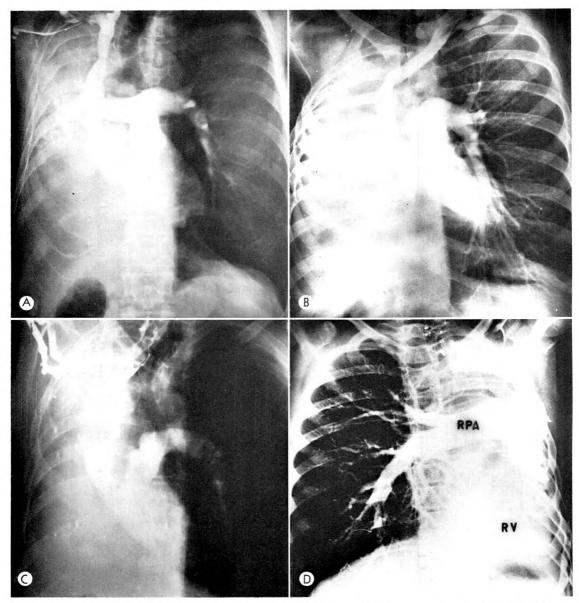


Fig. 10. Miscellaneous examples of pulmonary disease which may simulate agenesis of a lung. (A) Frontal angiocardiogram of a 64 year old man showing an intact right pulmonary artery with distortion of the pulmonary arterial branches by extensive pulmonary atelectasis due to cancer of the lung. (B) Frontal angiocardiogram of a 43 year old man made 6 weeks after pneumonectomy for lung cancer. Note that the right hemithorax contains fluid. The cardiovascular structures are still in the mid-line. (C) Frontal angiocardiogram of a 63 year old man with the superior vena cava syndrome which began 3 years following right pneumonectomy for lung cancer. Note the markedly deformed superior vena cava caused by recurrent lung cancer. The cardiovascular structures are rotated and the right pulmonary artery is absent. (D) Frontal angiocardiogram of a 9 year old girl who had had a left pneumonectomy for bronchiectasis 3 years previously. Note the rotation of the cardiac chambers and pulmonary artery into the left hemithorax. RV=right ventricle; RPA=right pulmonary artery.

lung can be impaired by significant associated congenital anomalies.

Angiocardiography is also valuable in the diagnosis of lobar agenesis of a lung. Anomalous, nonconstricting and hypoplastic pulmonary arteries of the right or the left lung can be demonstrated. This technique combined with bronchography is of benefit in the differentiation of acquired pulmonary disease such as the fibrothorax caused by bronchiectasis and tuberculosis from pulmonary agenesis. In massive atelectasis of a lung, angiocardiography, by revealing the distorted pulmonary vasculature, may be relied upon to establish the correct diagnosis. Finally, by showing the site of ligation and the stump of a pulmonary artery, pneumonectomy can be differentiated from pulmonary agenesis.

Israel Steinberg, M.D. The New York Hospital—Cornell Medical Center 525 East 68th Street New York, New York 10021

#### ADDENDUM

Since this paper was submitted for publication, another report on this subject was published by Jimenez-Martinez, M., Pérez-Alvarez, J. J., Pérez-Treviño, C., Rubio-Alvarez, V., and De Rubens, J. Agenesis of the lung with patent ductus arteriosus treated surgically: report of a case. 7. Thoracic & Cardiovasc. Surg., 1965, 50, 59-62.

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# POSTOPERATIVE PULMONARY PATTERNS FOLLOWING CARDIOPULMONARY BYPASS\*

By ARCH W. TEMPLETON, M.D.,† CARL H. ALMOND, M.D.,‡ ANTHONY SEABER,‡ CHARLES SIMMONS, M.D.,† and JAMES MACKENZIE, M.D.,‡ COLUMBIA, MISSOURI

THE use of the pump oxygenator and Cardiopulmonary bypass for open heart operations has increased the number of patients undergoing corrective cardiac procedures. Radiologists should be aware of the different postoperative pulmonary patterns which may be associated with procedures utilizing cardiopulmonary bypass. A knowledge of the possible underlying mechanisms producing the pulmonary findings will permit more meaningful roentgenographic interpretation. The radiologist is frequently the first person who has an opportunity to properly recognize an abnormal change, suggest its etiology, and thereby help instigate proper therapy.

In this study the different pulmonary patterns seen roentgenographically following cardiopulmonary bypass are presented. The underlying mechanisms for the pulmonary changes have been documented whenever possible. The significance of the findings is discussed. Cardiopulmonary bypass may be associated with problems in maintaining adequate circulation and oxygenation to the lung parenchyma. One group patients demonstrated pulmonary changes which are thought to be due to inadequate lung perfusion and resultant tissue anoxia and hemorrhage. Animal experiments have been conducted in which pulmonary anoxia produced pathologic findings similar to the pathologic findings found in 3 patients of this group.

# MATERIAL AND METHODS

The clinical and operative records and the postoperative roentgenograms of 70 consecutive patients undergoing cardiopulmonary bypass at the University of Missouri Medical Center up to July 1, 1965, were reviewed. The patients operated upon were of all ages and had a variety of cardiac lesions corrected. In all cases postoperative roentgenograms were available from the time the patient reached the recovery room to the time when all pulmonary changes had cleared or had resolved to a static condition. The chest roentgenograms were initially interpreted independent of clinical or operative history, and the changes, if any, were tabulated.

The possible factors in each cardiopulmonary bypass procedure which might contribute to postoperative roentgenographic changes were considered. The total time that the patient was on the cardiopulmonary bypass was recorded. Each perfusion was graded as excellent, good, fair, or poor. The grade was based on 5 variables. The first variable was maintenance of blood flow at or above 2.3 liters/m.2 of body surface area per minute at 30° C. The second factor was the successful maintenance of blood pressure at or above 70 mm./Hg. Untoward mechanical and technical pump errors lowered the perfusion grade. The fourth factor was cardiopulmonary bypass time. Lastly, the amount of blood transfused to maintain adequate flow and pressure was considered.

In addition, other preoperative or operative factors such as pre-perfusion hypotension or ventricular fibrillation, or variations in the perfusion technique, which might contribute to postoperative roentgenographic changes were noted. The operative procedure performed was recorded in all

<sup>\*</sup> From The Department of Radiology† and The Department of Surgery, Section of Thoracic and Cardiovascular Surgery,‡ University of Missouri Medical Center, Columbia, Missouri.

Table I
EIGHTEEN PATIENTS WITH NO POSTOPERATIVE CHEST CHANGES

No. of Patients	Procedures	Average Cardiopulmonary Bypass Time	Perfusion Grade	
4 9 2 1 1	Ventricular septal defect repair Atrial septal defect (secundum) repair Atrial septal defect (primum) repair Mitral valve replaced Complete correction of tetralogy of Fallot Isolated infundibular resection	40 min. 38 min. 1 hr., 46 min. 2 hr., 45 min. 1 hr., 5 min. 35 min.	Good (2) or excellent (2) Good (3) or excellent (6) Good Good Good Excellent	

cases. The data were combined to see if there were any consistent roentgenographic patterns which could be associated and correlated with certain perfusion or operative findings.

#### RESULTS

The 70 patients demonstrated 5 major categories of postoperative roentgenographic change. The first group of 18 patients had no significant postoperative chest findings (Table 1).

The second major category of 17 patients showed pulmonary parenchymal changes which are now thought to represent hemorrhage secondary to tissue anoxia (Table II). The pulmonary changes were bilateral in all instances and were characterized by ill-defined, variously sized areas of homogeneous infiltration. The infiltrates were usually present on initial recovery room roentgenograms but did not reach maximum severity for 24 to 48 hours. In most of the cases the lungs remained essentially unchanged for 5 to 6 days and then completely resolved during the next 8 to 10 days (Fig. 1, A–D).

The third group of characteristic pulmonary findings was seen in 6 patients who had operative lung contusion (Table III). These patients demonstrated moderate to severe confluent homogeneous opacification of a lung. In all instances, only I lung was involved. There was usually an associated small pleural effusion. These changes reached maximum severity within 3 to 6 hours following operation and slowly re-

gressed over an average period of 28 days (Fig. 2, A, B and C).

Sixteen patients formed a fourth group with a pattern of atelectasis, usually of the left lower lobe (Table 1v). The changes were usually maximal on the initial postoperative recovery room roentgenogram and cleared in 3 to 4 days (Fig. 3, A, B and C).

The remaining 13 patients formed the fifth major category. They all had abnormal findings demonstrated on postoperative roentgenograms but a characteristic pattern was not found (Table v). Six of these patients had widening of the superior mediastinum secondary to some degree of postoperative hemorrhage.

The three major groups showing roentgenographic patterns of anoxia, contusion or atelectasis were reviewed separately. The average time of maximal roentgenographic change was determined for each group as was the average time for complete resolution of these changes. Figure 4 shows the comparison of the average progression and regression of roentgenographic changes in relation to the average time of clearing for each of the three different groups.

### DISCUSSION

An ever increasing percentage of patients undergoing open heart operations has had no significant pulmonary findings. As seen from Table 1, these patients generally had a cardiopulmonary bypass time of less than 1 hour and a good to excellent perfusion grade. A large percentage of the patients

Table II seventeen patients with postoperative anoxic lung changes

Patient No.	Procedure	Bypass Time	Perfusion Grade	Possible Mechanisms of Anoxic Pulmonary Changes	
I	Removal of left atrial myxoma	1 hr., 6 min.	Good	Died—there was pre-pump shock and post- operative pressures could not be maintained	
2	Aortic valve replacement	1 hr., 55 min.	Fair	Large blood loss resulting in a fair perfusion	
3	Atrial septal defect repair	60 min.	Poor	60 sec. ventricular fibrillation before going into pump—hypotensive during anesthesia	
4	Aortic valve replaced and plastic repair of mitral valve	3 hr., 40 min.	Poor	Long, poor perfusion with 3,9∞ cc. blood loss	
5	Mitral valve replacement	2 hr., 23 min.	Fair	Fair perfusion with some difficulty in maintaining flow	
6	Mitral valvuloplasty	1 hr., 45 min.	Good	One right atrial catheter with clamping of main pulmonary artery	
7	Mitral valve replaced and aortic valvulotomy	2 hr., 58 min.	Good	Long pump run—severe tricuspid and aortic insufficiency postoperatively	
8	Mitral valve replaced	2 hr., 32 min.	Good	Died—one right atrial catheter with clamping of main pulmonary artery	
9	Mitral valve replaced	2 hr., 35 min.	Good	Two catheters in right atrium with clamping of main pulmonary artery	
10	Aortic valve replaced	2 hr., 04 min.	Good	Died—2 old myocardial infarcts—difficult maintenance of respiration and pressure during anesthesia	
11	Mitral valve replaced	3 hr., 05 min.	Good	Died—one right atrial catheter with clamping of main pulmonary artery	
12	Mitral valve replaced	2 hr., 55 min.	Good	One catheter in right atrium and main pulmo- nary artery clamped	
13	Mitral valve replaced; aortic and tricuspid valvuloplasty	3 hr., 35 min.	Fair	Long, fair perfusion—tricuspid insufficiency	
14	Aortic valve replaced	4 hr.	Good	One catheter in right atrium with pulmona artery clamped; hypotensive before bypa ventricular fibrillation before perfusion	
15	Ventricular septal defect repaired	1 hr., 55 min.	Poor	Hypotension before and intermittently throughout the perfusion	
16	Aortic valve replacement repaired	3 hr., 50 min.	Good	One catheter in right atrium with clamping of main pulmonary artery—long perfusion	
17	Mitral valve replaced	3 hr., 10 min.	Good	Long perfusion—also has ventricular septal defect with severe pulmonary hypertension	

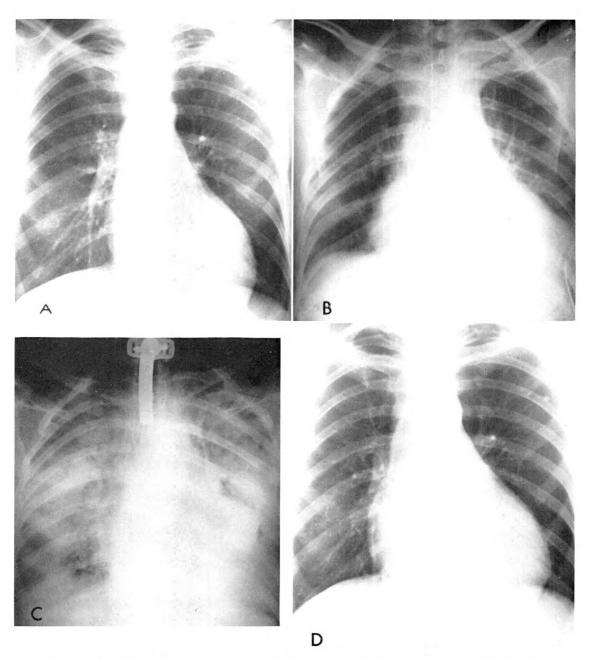


Fig. 1. Anoxic lung changes. The patient had an aortic valve prosthesis inserted. The total bypass time was 4 hours. The patient experienced ventricular fibrillation before the perfusion was started and the main pulmonary artery was clamped during the perfusion. (A) Preoperative chest roentgenogram showed clear lungs. (B) Roentgenogram taken 6 hours following the operation demonstrating bilateral haziness of the lungs. Superior mediastinal widening reflects some hemorrhage. (C) Roentgenogram exposed 48 hours following operation. There is a severe bilateral diffuse homogeneous lung infiltration. (D) Roentgenogram 15 days following the operation. The lungs are clear.

 ${\bf TABLE~III}$   ${\bf SIX~PATIENTS~WITH~POSTOPERATIVE~CHANGES~OF~CONTUSED~LUNG}$ 

Pa- tient No.	Procedure	Bypass Time	Perfu- sion Grade	Area of Lung Contused	Cause of Contused Lung
1	Total correction of tetralogy of Fallot	1 hr., 52 min.	Good	Right lower lobe	Chest tube
2	Repair of aortic prosthesis	58 min.	Excellent	Left lower lobe	Repair of aortic valve pros- thesis 12 mo. following in- sertion of the prosthesis
3	Mitral valve replaced	2 hr., 45 min.	Fair	Left mid and lower lung	Left thoracotomy; left phrenic nerve injured
4	Mitral valve replaced	2 hr., 50 min.	Good	Diffuse involvement of left lung	Previous mitral commissur- otomy
5	Mitral valve replaced	4 hr., 05 min.	G∞d	Diffuse involvement of left lung	Previous mitral commissur- otomy
6	Mitral valve replaced	1 hr., 51 min.	Fair	Left lung, particu- larly the lower lung	Previous mitral commissur- otomy

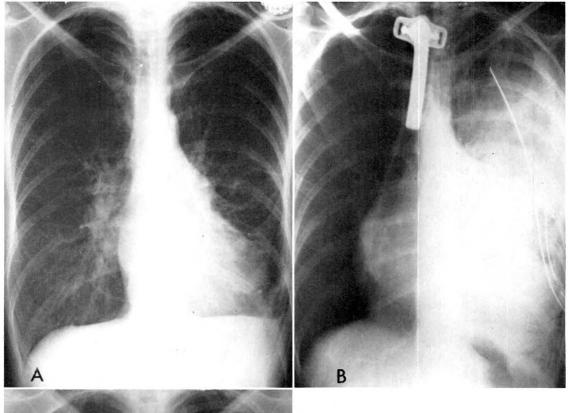
had uncomplicated congenital defects repaired.

However 74 per cent of the patients in this series had significant postoperative roentgenographic changes. Thirty-one per cent of the patients with positive postoperative roentgenograms had atelectasis, usually of the left lower lobe (Table IV).

The initial roentgenogram taken in the recovery room typically demonstrated a triangular density behind the heart with its base against the medial left hemidiaphragm with resultant obscuration of this portion of the hemidiaphragm (Fig. 3 B). Stimulation of the patient to cough and application of adequate suction resulted in

Table IV
SIXTEEN PATIENTS WITH POSTOPERATIVE ATELECTASIS

Patient No.	Procedure	Bypass Time	Perfusion Grade	Area of Atelectasis
I	Atrial septal defect repaired	30 min.	Good	Bilateral lower lobes
2	Atrial septal defect repaired	50 min.	Fair	Middle lobe
3	Aortic valve replacement	2 hr., 51 min.	Good	Left lower lobe
4	Atrial septal defect repaired	35 min.	Excellent	Left lower lobe
5	Tetralogy repaired	45 min.	Excellent	Left lower lobe
6	Aortic valve replacement	2 hr., 50 min.	Fair	Left lower lobe
7	Ventricular septal defect repaired	1 hr., 03 min.	Good	Left lower lobe
8	Tetralogy repaired	2 hr.	Fair	Bilateral lower lobes
9	Aortic valve replacement	3 hr., 20 min.	Fair	Left lower lobe
10	Aortic valve replacement	2 hr., 47 min.	Good	Left lower lobe
11	Atrial septal defect repaired	50 min.	Excellent	Left lower lobe
12	Atrial septal defect repaired	43 min.	Excellent	Left lower lobe
13	Aortic valvulotomy	1 hr., 43 min.	Excellent	Right upper lobe
14	Aortic valve replacement	2 hr., 21 min.	Fair	Left lower lobe
15	Mitral valve replacement	2 hr., 15 min.	Poor	Right lower lobe
16	Aortic valve replaced and small as- cending aortic graft	4 hr., 10 min.	Fair	Bilateral lower lobes



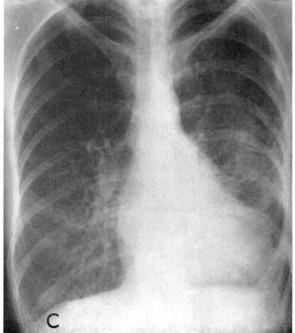
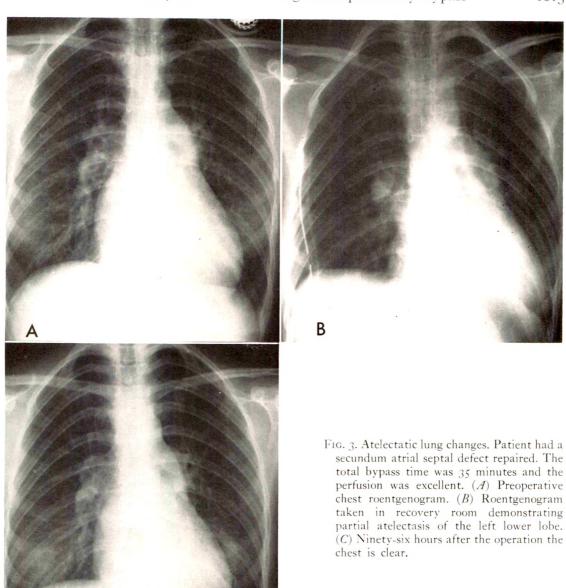


Fig. 2. Contusion lung changes. The patient had a mitral commissurctomy in 1961. The mitral valve was replaced with a prosthesis through a left thoracotomy in 1965. (A) Pre-open heart procedure chest roentgenogram showing old operative changes in the left lower lung and adjacent pleura. (B) Maximal changes of diffuse opacification of just the left lung are seen 12 hours following the operation. (C) Thirty-six days following the open heart operation. The left chest changes have slowly resolved to a static condition.



reaeration of the atelectatic portion of the lung within 48 to 96 hours.

Contused lung was recognized in 12 per cent of the patients (Table III). The characteristic roentgenographic findings were large confluent areas of homogeneous parenchymal infiltration limited to I lung (Fig. 2 B). Four of the 6 patients in this group had a previous operative procedure

in which the approach was through the left chest. Healing resulted in fibrotic changes in the lung, pleura and pericardium. When the subsequent open heart procedure was performed, extensive adhesions had to be dissected to allow adequate exposure of the heart. The trauma resulting from the dissection, as well as the parenchymal reaction to retraction, was the

 ${f T}_{f ABLE}\ {f V}$  thirteen patients with other postoperative chest changes

Patient No.	Procedure	Bypass Time	Perfusion Grade	Roentgenographic Changes
I	Aortic valve replacement	2 hr., 10 min.	Excellent	Wide superior mediastinum
2	Atrial septal defect repair and complete anomalous venous return corrected	2 hr., 22 min.	Good	Markedly widened superior medias- tinum
3	Atrial septal defect repaired	1 hr., 14 min.	Fair	Pneumonitis
4	Correction of pulmonary valve stenosis	26 min.	Fair	Wide superior mediastinum
5	Mitral valve replaced			Compressive atelectasis and pneu- monitis of right lower lobe? due to marked cardiomegaly
6	Aortic valve replaced	2 hr., 51 min.	Good	Left pleural effusion
7	Pulmonic valve stenosis repaired	29 min.	Good	Wide superior mediastinum
8	Atrial septal defect repaired	35 min.	Excellent	Right pleural effusion
9	Atrial septal defect and ventric- ular septal defect repaired	1 hr., 10 min.	Fair	Wide superior mediastinum
10	Repair of traumatic aortic aneurysm	1 hr., 45 min.	Good	Wide superior mediastinum; bilateral pleural effusion
. 11	Aortic valve replaced	2 hr., 05 min.	Good	Bilateral pleural effusion; bilateral pneumonitis
12	Mitral valvuloplasty	42 min.	Poor	Left pleural effusion; pneumonitis and atelectasis? left lower lobe pul- monary infarct
13	Prosthetic replacement of ascending aorta	1 hr., 15 min.	Good	Left pleural effusion with minimal compressive atelectasis and pneumonitis

mechanism for the contused lung. Hemostasis of the dissected tissues was poor and was a contributing factor. Therapy included intermittent positive pressure, aggressive suction, coughing, high humidity, and increased oxygen tension. To help eliminate the problem of contused lung, a different approach through the sternum or the right chest should be considered when a second major cardiac procedure is performed.

Thirty-one per cent of the patients with positive postoperative roentgenograms showed bilateral, ill-defined, variously sized areas of homogeneous lung infiltration (Fig. 1 C). These changes were originally thought to be compatible with pulmonary edema. However, the clinical course was not characteristic of pulmonary edema.

The onset was within the first 24 hours after the operation and there were shortness of breath and difficulty in respiration without rales or evidence of increased venous pressure. The symptoms coincided with the roentgenographic demonstration of infiltrations which progressed with the progression of the symptoms for 24 to 48 hours. The roentgenographic and clinical status of the patient remained essentially unchanged for 5 to 6 days and then returned to normal in the next 8 to 10 days. During this period of time, it was necessary to use positive pressure respiration with increased oxygen tension to maintain adequate ventilation for the patient.

Four of these 17 patients did not survive the postoperative period and an autopsy was obtained on 3. The lungs of these patients showed extensive intra-alveolar hemorrhage, swelling of the alveolar septa, chronic congestion, and in I case, complete necrosis of the lung tissue with hemorrhage (Fig. 5, A and B). Hypoxia before, during or following cardiopulmonary bypass was felt to be a significant factor in causing the diffuse hemorrhagic changes seen on both the roentgenograms and pathologic sections.

Animal experiments (dogs) in our laboratory subsequently demonstrated that cardiopulmonary bypass for I hour with a low blood flow rate maintained at 1,600 cc./m.2 of body surface area, a low oxygen concentration maintained at 70 per cent, and with complete occlusion of the main pulmonary artery would consistently produce bilateral hemorrhagic infiltrates in the lungs of the animals similar to that seen in the human autopsy material (Fig. 6, A and B). If the pulmonary artery was not clamped and either the blood flow increased to a normal of 2,400 cc./m.2 of body surface area or the oxygen increased to 100 per cent, pulmonary parenchymal hemorrhage did not occur following the I hour of cardiopulmonary bypass. While there are probably other factors which may produce hemorrhage into the pulmonary parenchyma, hypoxia is thought to be very important.<sup>3</sup>

Evaluation of the 17 cases demonstrated the following factors which could play a part in the production of pulmonary parenchymal hypoxia before, during or after perfusion. These factors included low preoperative blood pressures that were difficult to maintain after anesthesia was induced or ventricular fibrillation with decreased arterial pressure before being placed on the cardiopulmonary bypass. The length of the perfusion time seemed to be a factor but was not as critical as one might assume. The maintenance of perfusion blood pressure and flow with adequate oxygenation appeared to be quite critical. Technical errors during perfusion could be disastrous but were not a deciding factor in the 17 patients. Seven of the 17 cases had the pulmonary artery clamped during the period of cardiopulmonary bypass. In these patients both lungs were perfused solely by

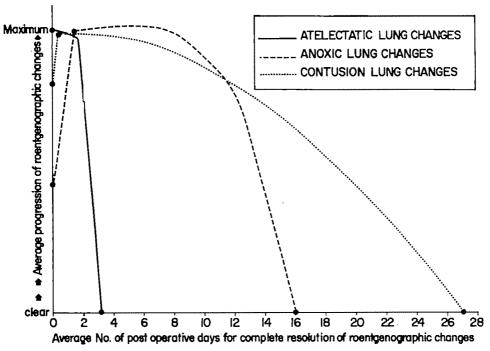


Fig. 4. The average progression and regression of roentgenographic changes for the 3 groups of patients with anoxic, atelectatic, or contusion lung changes are related to time.

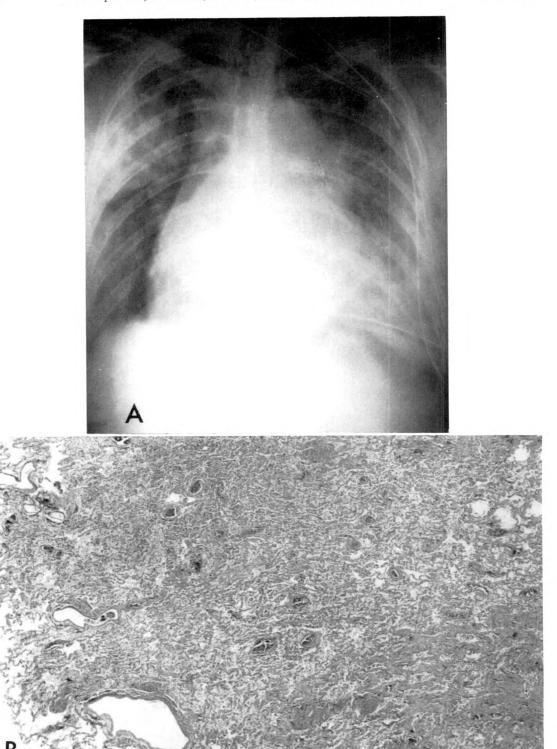


Fig. 5. Patient who died 48 hours following replacement of the mitral valve. The perfusion was good. Total bypass time was 3 hours and 5 minutes and the main pulmonary artery was clamped. (A) Roentgenogram taken 12 hours after operation demonstrates bilateral coalescent homogeneous infiltrates. (B) Photograph of lung section showing diffuse red blood cell infiltration throughout the lung parenchyma.

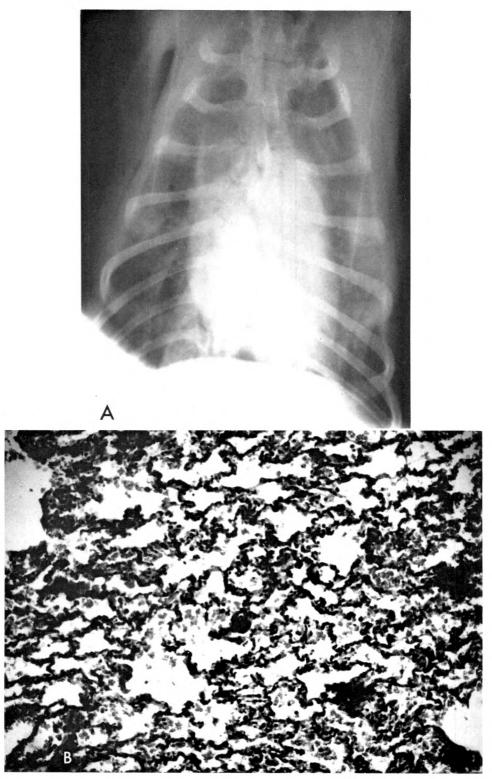


Fig. 6. (A) Roentgenogram of dog 6 hours after cardiopulmonary bypass with the main pulmonary artery clamped and low oxygen concentration and blood flow rate. The lungs show bilateral homogeneous infiltration. (B) The animal died after 13 hours and the photograph of a lung section revealed generalized intra-alveolar hemorrhage similar to that seen in the human lung (Fig. 5B).

the bronchial supply, and lung nutrition was thus very dependent on good systemic blood pressures and flow as well as funcbronchial-pulmonary moses.2,4,5 The cardiac output during the postoperative period was also a critical factor in maintaining adequate tissue perfusion and oxygenation.

In 25 per cent of patients with abnormal chest roentgenograms, the changes were nonspecific and could not be correlated with a specific etiologic mechanism. Mediastinal widening due to postoperative hemorrhage was seen in patients who had replacement of the aortic valves, ventricular or atrial septal defects repaired, or pulmonic valve stenoses corrected.

#### CONCLUSION

The postoperative chest roentgenograms of 70 patients undergoing cardiopulmonary bypass for an open heart procedure have been reviewed. These findings have been correlated with the patients' operative course, and 3 distinct roentgenographic pulmonary patterns due to atelectasis, operative lung contusion, or anoxia induced parenchymal hemorrhage have been identified. Another group of patients had various postoperative chest findings but a common etiologic factor could not be found. An increasing percentage of patients has failed to show any significant postoperative pulmonary change.

The concept of tissue anoxia, secondary

to inadequate lung parenchyma perfusion, resulting in hemorrhagic changes was initially suggested by pathologic findings in 4 patients who succumbed in the postoperative period. Identical pathologic lung alterations have been reproduced in animal experiments. The various causes of decreased tissue perfusion are discussed.

By recognizing the different roentgenographic pulmonary patterns seen in patients undergoing cardiopulmonary bypass procedures, the radiologist can suggest the underlying pathologic process and thereby make a significant contribution towards the successful management of the patient.

Arch W. Templeton, M.D. University of Missouri Medical Center Columbia, Missouri 65202

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### SUBPULMONARY PNEUMOTHORAX\*

By GERALD J. KURLANDER, M.D., and CHARLES H. HELMEN, M.D. INDIANAPOLIS, INDIANA

IN A RECENT publication, Fleischner¹ has explained in some detail the mechanisms for the variation in locations of free pleural fluid. The same mechanisms apply to unusual locations of pneumothorax—specifically subpulmonary pneumothorax. We have observed several instances of subpulmonary distribution of free pleural gas. This brief communication is presented to emphasize the roentgen features of subpulmonary pneumothorax and to add further roentgen confirmation to the theory of pleural pressure dynamics as suggested by Fleischner.

#### ILLUSTRATIVE CASES

Case I (12-04-38). D.G., a 25 year old white female, was admitted with the diagnosis of bronchopneumonia. A frontal chest roentgenogram indicated bilateral basilar bronchopneumonia (Fig. 1A). An attempt to aspirate fluid from the left pleural cavity was unsuccessful. A frontal chest roentgenogram made immediately following the thoracentesis (Fig. 1B) demon-

strated the presence of a crescentic gas collection in the base of the left pleural cavity with some extension of gas laterally about the diseased lower lobe.

Case II (35-39-26). A.H., a 24 hour old female infant, weighed 6 pounds, 6 ounces at birth. The mother had a normal pregnancy and a normal vaginal delivery. At the time of birth the condition of the patient appeared good but at 20 hours of age the respiratory rate was noted to be rapid and the infant refused feedings of glucose water. Frontal and lateral chest roentgenograms (Fig. 2, A and B) at this time demonstrated a subpulmonary gas lucency on the left with loss of volume of the left lower lobe. The subpulmonary gas was seen beneath the left lower lobe in the lateral projection. In addition, mediastinal gas was seen in the anterior mediastinum on the lateral projection. Roentgenograms of the chest 7 days later were considered to be normal.

Case III (37-09-19). P.B. was a 31 hour old term male infant. At approximately 27 hours of age the patient was noted to be slightly cyanotic and tachypneic. The patient was then referred

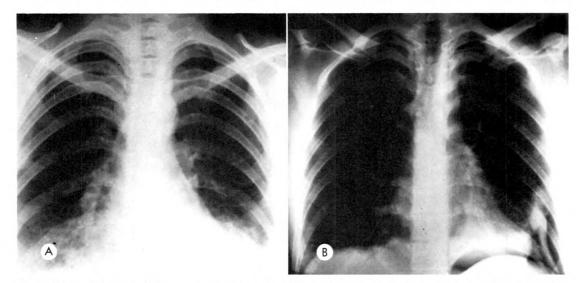


Fig. 1. Case I. (A) Frontal chest roentgenogram shows bilateral basilar bronchopneumonia. (B) Frontal chest roentgenogram immediately after thoracentesis shows the crescentic gas lucency of subpulmonary pneumothorax. Intrapleural gas can be seen extending laterally about the diseased lower lobe.

<sup>\*</sup> From the Department of Radiology, Indiana University Medical Center, Indianapolis, Indiana.

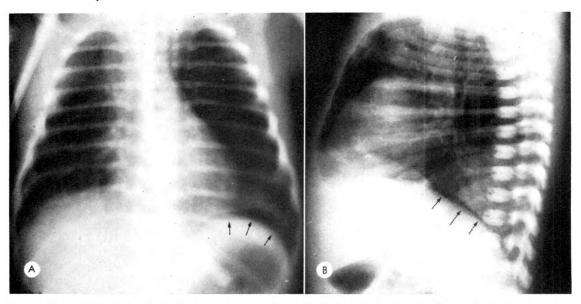


Fig. 2. Case II. (A) Frontal chest roentgenogram shows the crescentic gas lucency (arrows) of subpulmonary pneumothorax. (B) Lateral chest roentgenogram shows free intrapleural gas (arrows) beneath the incompletely expanded left lower lobe. The retrosternal lucency is indicative of pneumomediastinum.

to the Indiana University Medical Center. Physical examination at the time of admission showed an overactive apical impulse which was palpated adjacent to the right nipple. A frontal chest roentgenogram (Fig. 3) demonstrated dextrocardia, crescentic shaped subpulmonary pneumothorax on the left associated with infiltration and loss of volume of the left lower lobe. In addition, there was evidence of pneumomediastinum. The cardiac silhouette was located in the right hemithorax. During the next 2 weeks the cyanosis disappeared and the respiratory rate returned to normal. The cardiac diagnosis based on physical examination, chest roentgenograms, and electrocardiogram was dextrocardia, ventricular septal defect, and possible pulmonary stenosis.

#### DISCUSSION

The normal lung remains expanded because it is subjected to atmospheric pressure via a patent tracheobronchial tree and because the intrapleural pressure is slightly less than atmospheric pressure. In the presence of pneumothorax, a healthy lung will retract in a nearly symmetric fashion around its periphery, tending to preserve the normal configuration. If a lobe of the lung is diseased, this symmetric collapse pattern may not occur in the presence of

pneumothorax. Blood, exudate, mucosal edema, or any intrabronchial material may obstruct the smaller bronchi of a lobe to produce some degree of lobar collapse. Except when the lobe is completely consolidated, lobar collapse greatly enhances the retractile tendency of the lobe. A pneumothorax under these circumstances will tend to collect around this lobe even if the patient is in the upright position and the lobe

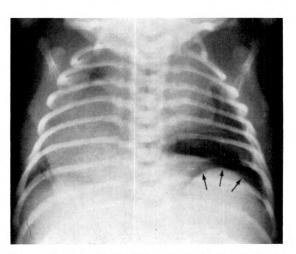


Fig. 3. Case III. Frontal chest roentgenogram shows dextrocardia, pneumomediastinum, and subpulmonary pneumothorax (arrows).

involved is a lower lobe. Here the atelectatic tendency of the diseased lower lobe resists "re-expansion more than the rest of the lung." In the patients described above, all had evidence of disease of the left lower lobe and all had the crescentic gas lucency indicative of subpulmonary pneumothorax. The upper margin of this lucency corresponds to the lower lobe with its visceral pleural covering and the lower margin corresponds to the diaphragm with its parietal pleural covering.

Subpulmonary pneumothorax when present on roentgenograms made in the upright position may be confused with free intraperitoneal gas. Since pneumonia, particularly of the lower lobe, can simulate acute abdominal disease, the correct interpretation of the gas lucency is of the utmost importance. Often some free gas may be seen about the lateral margin of the lower lobe to establish the diagnosis of pneumothorax. If a crescentic gas lucency is seen in the presence of lower lobe disease, subpulmonary pneumothorax should be the first consideration rather than free intraperitoneal gas. A right or left lateral debubitus roentgenogram of the lower chest and upper abdomen using a horizontally directed roentgen-ray beam should provide definitive differentiation in questionable cases.

An early roentgen sign of spontaneous rupture of the esophagus is the "V" sign of Naclerio. This is a V-shaped radiolucency

in the lower thorax which corresponds to gas in the fascial planes of the mediastinum and diaphragmatic pleura in the region of the lower esophagus. There should be no confusion between this lucency and subpulmonary pneumothorax. The former gas collection is always accompanied by mediastinal emphysema and is usually present in very small amounts, occasionally detectable on routine chest roentgenograms. Rarely, if ever, does the gas in the fascial planes of the diaphragmatic pleura extend to the lateral margin of the diaphragm.

#### SUMMARY

Subpulmonary pneumothorax is a rather frequent localization of free intrapleural gas when there is disease in the lower lobe of the lung. Its mechanism and roentgen features are briefly outlined.

Gerald J. Kurlander, M.D. Department of Radiology Indiana University Medical Center 1100 West Michigan Street Indianapolis, Indiana

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# BILATERAL TUBERCULOUS MEDIASTINAL LYMPHADENOPATHY IN THE ADULT

By RICHARD D. KITTREDGE, M.D., and NATHANIEL FINBY, M.D. NEW YORK, NEW YORK

PARENCHYMAL pulmonary tuberculosis, though minimal, may be accompanied by lymph node infection. Commonly, tuberculous peribronchial lymph nodes will correspond to the site of drainage from the parenchyma. When the infection is more severe, the ipsilateral paratracheal lymph nodes and the lymph nodes at the bifurcation of the trachea become involved. In overwhelming infection, spread to the lymph nodes of the opposite side may occur so that a primary infiltrate in one lung can be accompanied by massive bilateral mediastinal lymphadenopathy. In children, caseation is more marked in lymph node tissue than in pulmonary lesions. Gradually, as lymph node tissue heals, caseation disappears and deposition of calcium occurs.

The association of pulmonary and lymphatic tuberculous infection in childhood is referred to as the primary complex. One of the first to call attention to this was Ghon<sup>2</sup> in 1916. This primary complex can present again in adult life as lymph node involvement with or without visible pulmonary disease. Although the adult counterpart of the primary childhood complex is a very different stage of the disease in the host, nevertheless, the roentgenographic appearance is quite similar as long as the lymph nodes correspond to the drainage site of the involved parenchyma. Massive bilateral lymphadenopathy without parenchymal pulmonary lesions, though more commonly seen in children, occasionally will occur in the adult. It is sufficiently rare so that tuberculosis may not be considered in the initial differential diagnosis.

Massive involvement of the thoracic lymph nodes may be accompanied by serious clinical problems. Large tuberculous lymph nodes can narrow the luminal diameter of the main bronchi and trachea at the bifurcation. Such narrowing of the lumen

may secondarily cause involvement of parenchyma. Active tuberculous lymph nodes may infect a bronchial wall by direct contact, causing rupture into the bronchus and considerable destruction of the bronchial structure. Occlusive changes in segmental portions of lung will then follow. This type of secondary bronchial involvement with peripheral parenchymal collapse and infection is not uncommon. It is interesting to note that it is common to find a small parenchymal infiltration in one part of a lung with subsequent collapse of an entirely separate portion of the lung due to bronchial involvement by massive mediastinal lymph nodes. This is often seen in children who do not successfully control their primary complex. The peripheral collapse does not represent spread of active parenchymal infection but is purely mechanical involvement of the bronchus.

It has been noted by MacPherson and Lutwyche<sup>3</sup> that of 28 cases of collapse associated with primary lesions, in 26 the collapse had re-expanded within a 3 year period. It is not uncommon for re-expansion to occur within I to 2 years following treatment of the bronchial lesion. Unquestionably, tuberculous erosion of the bronchial system will spread peripherally into the lung parenchyma and cause infection. An acute rupture can thus precipitate bronchotuberculous pneumonia. whelming tuberculous pneumonia following a bronchial rupture has been described by Brock, Cann and Dickinson.<sup>1</sup>

The visceral lymphatic nodes of the tracheobronchial tree are divided into the following groups: (1) The tracheal group; that is the paratracheal lymph nodes along the tracheal air column. (2) The tracheobronchial group extending downward onto the surface of the main bronchi, dividing into the groups described on the right and

left main bronchi. They are connected with anterior and posterior mediastinal lymph nodes and drain to the paratracheal lymph nodes and the deep cervical lymph nodes. (3) The bifurcation group of lymph nodes is wedged in the tracheal bifurcation and extends downward on either side to the beginning of the lower lobe bronchi. They drain to the tracheobronchial lymph nodes and are connected with the posterior mediastinal lymph nodes. (4) The bronchopulmonary lymph nodes lie in the angles between the branches of the bronchial tree. The nodes vary considerably in number and they drain to the tracheobronchial lymph nodes and the lymph nodes of the bifurcation. (5) Pulmonary lymphatic nodes lie in the lung tissue, usually in the angles between two bronchial tubes. Beyond this point the existence of true lymphatic nodes is very doubtful, although it is stated that peripheral lymphatic tissue can be found.

Certain groups of lymph nodes are more easily seen when enlarged due to their position (Fig. 1). These are: (1) The right paratracheal lymph nodes; (2) the left tracheal bronchial lymph nodes between the aortic knob and the left pulmonary artery; (3) the right paratracheal lymph nodes lying above the right pulmonary artery in close relationship to the epiarterial bronchus; (4) the right bronchopulmonary lymph nodes which lie to the outer side of the pulmonary artery (the left bronchopulmonary lymph nodes are less well placed for observation, being hidden beneath the left border of the heart); and (5) the retrosternal lymph nodes.

Lymph node enlargement can be divided easily into two categories: (a) Gross enlargement with individual lymph nodes and groups of lymph nodes projecting into the lung fields from the mediastinum and overlapping the normal vascular structures of the hilus. Roentgenographically, this presents a characteristic scalloped contour; and (b) slight widening of the mediastinum without a scalloped outline. In this type accurate diagnosis is difficult; lateral and oblique views will often help.

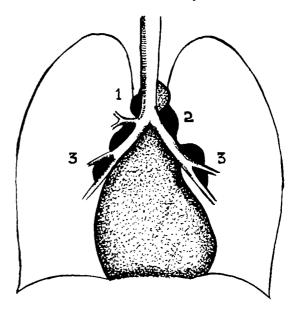


Fig. 1. Certain groups of lymph nodes due to their position are more easily seen when enlarged. They are: (1) Right paratracheal lymph nodes; (2) lymph nodes between the aortic knob and pulmonary artery; and (3) bronchopulmonary lymph nodes in the hilar areas.

The clinical symptomatology associated with large masses of caseating tuberculous lymph nodes is characterized by malaise, loss of weight, irregular pyrexia and anorexia. Characteristic physical findings will occur when collapse of a lung or part of a lung occurs.

Classically, treatment of hilar lymphadenitis is not unlike that of parenchymal tuberculous infection. Healing of the caseous mass of lymph nodes is a prime objective. Chemotherapy and rest are the basis of the therapeutic armamentarium. When there is a partial or complete collapse of a part of a lung, bronchoscopy, to reopen a bronchus by removal of granulation tissue or tuberculous lymph node material, may be necessary. However, since the lung reexpands after 1 to 2 years of proper treatment, in a large number of cases mechanical intervention is usually not needed.

The cases below are presented because massive bilateral lymphadenopathy in the adult is not a common initial manifestation of active tuberculous disease. When this



Fig. 2. Case I. Roentgenogram of the chest shows marked bilateral paratracheal and bronchopulmonary lymph node enlargement.

does occur, the roentgen appearance is often misinterpreted as lymphoma, sar-coidosis or other nontuberculous infection.

#### REPORT OF CASES

Case I. This was the first hospital admission of a 4I year old Haitian Negro male with the chief complaint of episodic chest pain over a 3 week period. The patient had had intermittent fever and fatigue for 10 months prior to admission and a weight loss of 10 to 15 pounds, a productive cough for 6 months and 3 weeks of chest pain.

Physical examination showed a temperature of 100.2° F., pulse 88 and regular. The patient appeared to be a well developed male in no distress. Physical findings of note were bilateral submaxillary, axillary, inguinal and posterior cervical lymph node enlargements. Examination of the lungs revealed some splinting and a pleural friction rub on the left. The heart was normal and the abdomen was unremarkable.

In the hospital, there was a markedly pustular positive reaction to intermediate PPD. A roentgenogram of the chest demonstrated marked bilateral paratracheal and bronchopulmonary lymph node enlargement without parenchymal infiltrate (Fig. 2). Left supraclavicular lymph node biopsy showed caseating

granulomata. Tuberculous culture of the biopsied lymph node was positive. Six months following therapy, a chest roentgenogram showed the hilar lymphadenopathy much decreased (Fig. 3).

Discharge diagnosis was tuberculous lymphadenitis.

Case II. This was the first hospital admission of a 26 year old Negro male truck driver admitted from the Emergency Room because of chest pain of 6 months' duration with 3 days of chills and fever.

In August, 1957, four years prior to admission, the patient was hospitalized elsewhere with a febrile illness associated with left flank pain. The diagnosis of left renal infection and abscess was made and the patient was treated with large doses of penicillin and acromycin with resolution of fever and eventual disappearance of roentgenographic evidence of a mass in the upper pole of the left kidney.

In April and November of 1960, he was admitted to the hospital on separate occasions for multiple complaints. Work-up proved essentially negative. In May, 1961, he began to complain of pain in the left upper abdomen with tenesmus and frequent passage of mucus by rectum. He complained also of pressure in the thorax to the right of the sternum with pain on coughing and deep breathing radiating to the



Fig. 3. Case I. Six months after therapy the chest roentgenogram shows marked improvement,

intrascapular region of the back. The patient was treated with antispasmodics and tranquilizers with no relief of symptoms. Throughout the summer, gastrointestinal and chest symptoms persisted with increasing malaise and fatigue. The patient continued to work as a truck driver. Twelve days prior to admission he appeared in the Emergency Room with a temperature of 100°F. and pleuritic pain in the right chest of increased severity for 2 days. A roentgenogram of the chest was unremarkable and the patient was discharged with symptomatic treatment and referred to Medical Clinic. Two days prior to admission, the patient returned to the Emergency Room complaining of chills, fever, myalgia and pain in the chest. His temperature was 103°F.; physical examination was otherwise unremarkable. Blood cell count showed a hemoglobin of 13.4 gm. per cent, and 23,500 white blood cells, with 86 per cent polymorphonucleocytes, 9 per cent lymphocytes, 3 per cent mononucleocytes and 2 per cent basophils. A chest roentgenogram showed fullness in the space beneath the aortic knob and both hilar areas, suggesting bilateral lymphadenopathy. No infiltrate was present (Fig. 4). The patient was admitted to the hospital.

Physical examination revealed a well nour-

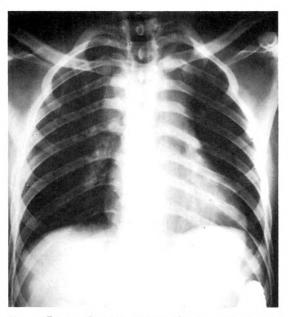


Fig. 4 Case II. Roentgenogram shows a tumor mass of the right paratracheal area with fullness in the space beneath the aortic knob and both hilar areas. Bilateral lymphadenopathy was strongly suggested.



Fig. 5. Case 11. Three years following therapy, the chest roentgenogram shows marked regression with return towards normal.

ished male, feverish, and acutely ill. His temperature was 104.8°F., pulse 100, respirations 32, with a blood pressure of 120/80. His lymph nodes appeared moderately indurated, most marked in the cervical and axillary areas. Chest, abdomen and the remainder of the examination were within normal limits. Serial sputums for acid fast bacilli were negative. The patient was placed on symptomatic treatment with salicylates while clinical evaluation was started. Skin test performed on the first hospital day revealed the following: OT(1-1000) positive after 48 hours; hystoplasmin positive after 48 hours; coccidioidin positive in 24 hours, and blastomycin equivocal. A scout roentgenogram of the abdomen showed calcification within the spleen and an esophagram revealed extrinsic pressure at the level of the mid-esophagus. This plus the presence of widening of the superior mediastinum was felt to indicate the presence of mediastinal lymphadenopathy.

During the first hospital week, the patient continued to have temperature spikes of 104 to 105°F. daily; initial culture and blood studies failed to provide an etiologic explanation for this febrile illness.

Serial chest roentgenograms demonstrated progressive enlargement of the superior mediastinal shadow with beginning infiltration in the right upper lobe. A right axillary lymph node biopsy showed chronic lymphadenitis. The progressive enlargement of the mediastinal lymph nodes without major accompanying parenchymal disease was felt to be most compatible with the diagnosis of lymphoma. Such a course is seen in primary tuberculosis of childhood, but would be rare in a 26 year old man.

With the diagnosis still very much in doubt and definitive treatment still an open question, it was felt that there was no alternative but to perform exploratory thoracotomy and medias-

tinal lymph node biopsy.

The biopsy material contained lymph nodes almost entirely replaced by caseous material. The pathologic report was tuberculous lymphadenitis. The patient was started on triple tuberculosis therapy with gradual fall in temperature. He remained afebrile during the remainder of the hospital stay.

The final diagnosis was generalized lymphadenitis, chronic and acute, of tuberculous etiology. Three years following therapy, the chest roentgenogram showed marked improvement (Fig. 5).

#### SUMMARY

Massive bilateral tuberculous mediastinal lymphadenopathy in the adult is sufficiently rare so that the etiology may not be included in the initial differential diagnosis. When the clinical course indicates infection, tuberculosis should be suggested.

Richard D. Kittredge, M.D. Department of Radiology St. Luke's Hospital 113th St. and Amsterdam Avenue New York 25, New York

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# WIDENING OF THE LEFT PARAVERTEBRAL PLEURAL LINE ON SUPINE CHEST ROENTGENOGRAMS IN FREE PLEURAL EFFUSIONS\*

By RICHARD T. TRACKLER, M.D., and RAY A. BRINKER, M.D. ST. LOUIS, MISSOURI

THE distribution of free pleural effusions on supine, overexposed chest roentgenograms is imperfectly understood. At the Mallinckrodt Institute of Radiology, a supine anteroposterior overexposed grid roentgenogram is a part of the routine chest examination. We have analyzed the appearance of pleural effusions on the chest roentgenograms of 100 patients with particular reference to the examination in this view.

#### HISTORIC REVIEW

The authors reviewed the English language roentgen literature since its inception.

In a translation of Barjon's<sup>1</sup> "Radiodiagnosis of Pleuropulmonary Affections," Honeij in 1918 described the appearance of pleural effusions on routine chest roentgenograms in the upright position.

Rigler<sup>18,14</sup> clearly described the redistribution of pleural effusions with a change of the patient's position from the upright to the supine and the lateral decubitus positions. He noted that in the supine position the fluid shifts to the dependent part of the thorax with a resultant hazy density distributed over the entire hemithorax. Felson,4 Fleischner,6 Hessén9 and Petersen12 have also described the appearance of free pleural effusions in the supine view as a homogeneous haze of the entire lung field contrasting with the opposite lung field. With larger quantities of fluid, a thin band of fluid may be seen along the lateral margins and the apex of the affected lung as well.

Lachman,<sup>10</sup> in an analysis of the topography of the human thorax, illustrated and

discussed the paravertebral pleural reflection lines which are due to the posterior mediastinal boundaries of the lung and pleurae (Fig. 1). Garland<sup>8</sup> also concluded that the paravertebral linear shadows, seen more often on the left side than on the right side of the lower half of the thoracic spine, were due to a tangential projection of the borders of the lung and adjacent pleural covering. Brailsford<sup>2</sup> elaborated on the significance of widening of the posteromesial pleural line or linear thoracic paraspinal shadow. He noted that the paraspinal line will be displaced laterally by any expansion of tissue medial to it. Vertebral body fractures, paravertebral hematomas, paravertebral abscesses and primary and secondary neoplasms of vertebral bodies producing increased transverse diameter of the vertebra may all widen the paraspinal pleural line.

Dalton and Schwartz<sup>3</sup> described widening of the left paraspinal pleural line in cases of aneurysm and dilatation of the aorta due to pulling of the pleural surface away from the vertebral bodies. Paul and Juhl<sup>11</sup> discussed local or general mediastinal widening when pleural fluid is loculated at the mediastinum.

#### MATERIAL REVIEWED

The authors reviewed 100 consecutive cases of pleural effusions. Serial roentgenograms, when available, were reviewed for evaluation of the position of the paravertebral pleural line during the evolution and resolution of free pleural effusions. Posteroanterior erect (Fig. 2), left lateral erect, and supine anteroposterior overexposed grid roentgenograms (Fig. 3) were routinely

<sup>\*</sup> From the Edward Mallinckrodt Institute of Radiology, Washington University, St. Louis, Missouri.

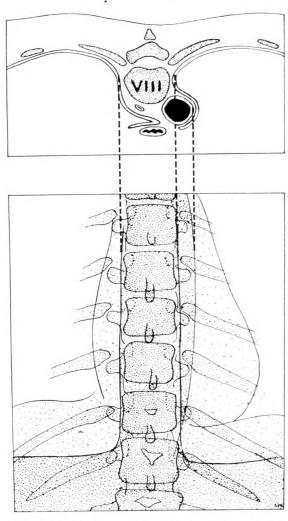


Fig. 1. Above: Cross-section through the posterior mediastinum at the level of the eighth thoracic vertebra. Below: Diagram taken from a roent-genogram depicting the posterior portions of the visceral and/or parietal pleura as lines along the vertebral column. Dotted lines indicate anatomic substrates of pleural lines and aortic lines in cross-section. (Reproduced by permission from Anat. Rec., 1942, 83, 526.)

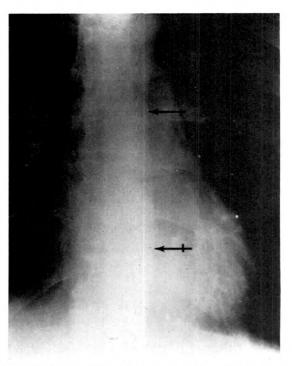


Fig. 2. A normal posteroanterior erect chest roentgenogram. The aorta (++) is in normal position. The left paravertebral line is not seen.

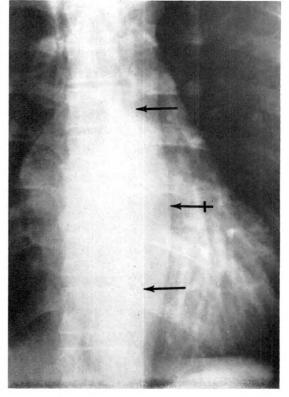


Fig. 3. A normal supine anteroposterior overexposed grid roentgenogram. The left paravertebral line (←) and aorta (←) are in normal relationship.

reviewed. Roentgenograms taken in the lateral decubitus position with horizontal beam were evaluated when available.

#### REPORT OF CASES

Case I. J.G., a 57 year old white housewife, was admitted to Barnes Hospital for evaluation of biopsy proven anaplastic carcinoma metastatic to the left supraclavicular lymph nodes. The left hilus was enlarged and an infiltrate in the left upper lobe was identified. The patient had numerous diagnostic examinations which did not establish another primary site for the tumor. Subsequently, she had both betatron and cobalt 60 teletherapy to the tumor sites in the lung and in the left supraclavicular region. A posteroanterior erect roentgenogram obtained on May 18, 1965, (Fig. 4A) 18 days after

the termination of radiation therapy, demonstrated an interval regression of the left upper lobe infiltrate and of the left hilar lymph nodes. A supine anteroposterior overexposed grid roentgenogram of May 18, 1965, (Fig. 4B) demonstrated the left paravertebral pleural line and descending aortic shadows in normal relationship. On June 7, 1965, it was established on both inspiration and expiration roentgenograms and by fluoroscopy that the patient had a fixed, elevated left hemidiaphragm. Figure 4C shows the elevated left hemidiaphragm in a posteroanterior erect view. The left paravertebral pleural line is widened on the supine anteroposterior overexposed grid roentgenogram of June 7, 1965 (Fig. 4D), suggesting a free pleural effusion as well. A left lateral decubitus roentgenogram (Fig. 4E), taken on

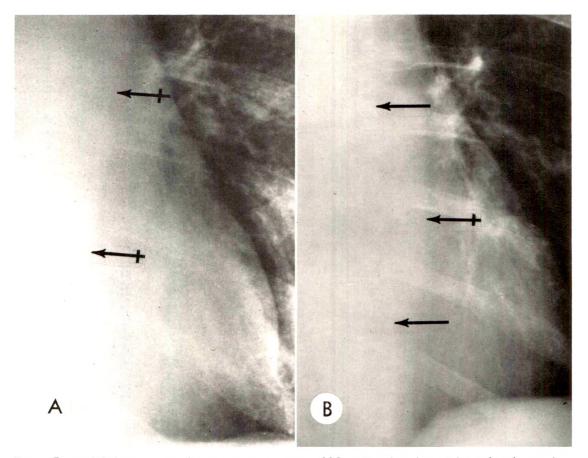
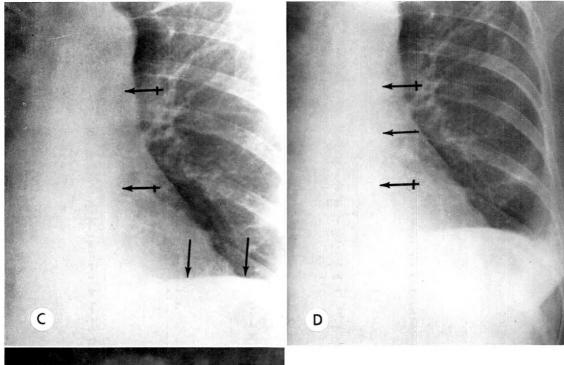


Fig. 4. Case I. (A) A posteroanterior erect roentgenogram of May 18, 1965, taken 18 days after the termination of radiation therapy to the left lung and the left supraclavicular region. The aorta  $(\longleftrightarrow)$  is in normal position. The left paravertebral line is not identified. (B) A supine anteroposterior overexposed grid roentgenogram May 18, 1965, demonstrating a normal relationship of the left paravertebral line  $(\leftarrow)$  and aortic shadow  $(\hookleftarrow)$ .



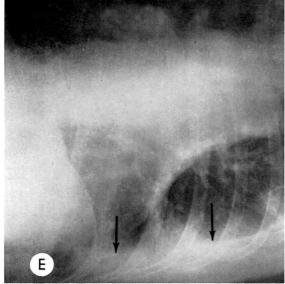


Fig. 4. (C) A posteroanterior erect roentgenogram of June 7, 1965 demonstrating a fixed, elevated left hemidiaphragm (↓↓). The left paravertebral line is not seen. The aorta (↔) is only faintly demonstrated. (D) A supine anteroposterior overexposed grid roentgenogram of June 7, 1965, demonstrating an interval widening of the left paravertebral line (←) which now blends with the more anteriorly placed aortic line (←), suggesting a free left pleural effusion. (E) A left lateral decubitus roentgenogram of June 7, 1965 demonstrating free pleural fluid (↓↓) in the left hemithorax.

the same day, confirmed the presence of a small, free, left pleural effusion.

Case II. P.E.M., a 19 year old white male, was admitted to Barnes Hospital for evaluation of "hypercoagulability state." The patient had a history of embolization to the right lung followed by ligation of the inferior vena cava on December 3, 1964. A supine anteroposterior overexposed grid roentgenogram of December

28, 1964, (Fig. 5A) showed the left paravertebral pleural line to be normal.

The patient had left-sided pleuritic pain, cough and hemoptysis before the posteroanterior erect roentgenogram (Fig. 5B) and the supine anteroposterior overexposed grid roentgenogram (Fig. 5C) were made on January 20, 1965. There was an infiltrate in the left midlung field. The left costophrenic sulcus was unsharp in the posteroanterior erect view. The left

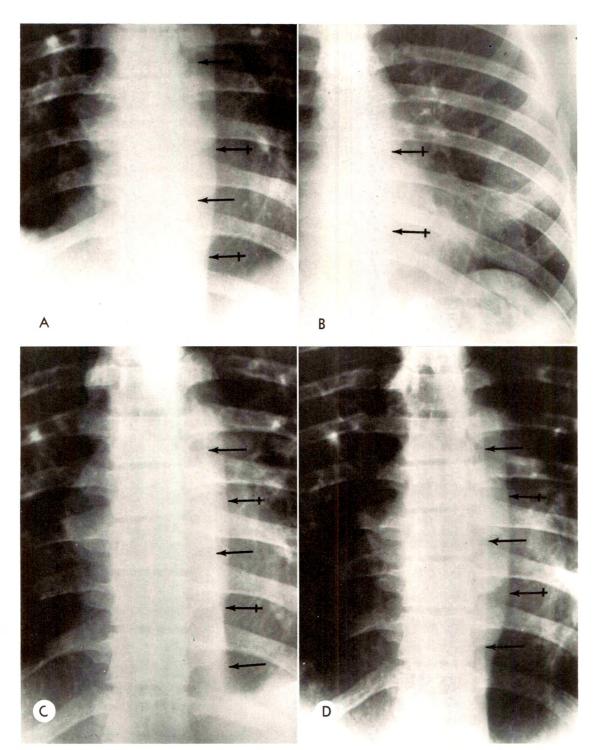
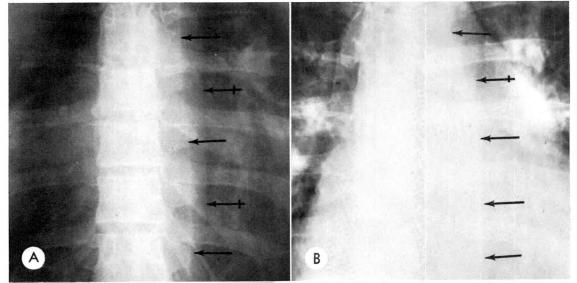


Fig. 5. Case II. (A) A supine anteroposterior overexposed grid roentgenogram of December 28, 1964, demonstrating a normal relationship of the left paravertebral line ( $\leftarrow$ ) and the aorta ( $\leftrightarrow$ ). (B) A posteroanterior erect roentgenogram of January 20, 1965 shows a left midlung field infiltrate and fluid in the left costophrenic sulcus. The left paravertebral line was only faintly demonstrated on the original roentgenogram. The aorta ( $\leftrightarrow$ ) is in normal position. (C) A supine anteroposterior overpenetrated grid roentgenogram of January 20, 1965 demonstrating widening of the left paravertebral line ( $\leftarrow$ ) in relationship to the aortic shadow ( $\leftrightarrow$ ). (D) A supine anteroposterior overexposed grid roentgenogram of January 29, 1965 demonstrating return of the left paravertebral line ( $\leftarrow$ ) to its normal position in relationship to the aorta ( $\leftrightarrow$ ). The patient was asymptomatic.

paravertebral pleural line was in normal position. On the supine anteroposterior overexposed grid roentgenogram there was widening of the left paravertebral line consistent with free pleural effusion. The patient became clinically asymptomatic and felt well at the time the supine anteroposterior overexposed grid roentgenogram of January 29, 1965, (Fig. 5D) was made. The left paravertebral pleural line had returned to its normal position.

CASE III. M.R.A., a 29 year old white female,

developed progressive uremia over the 4 years prior to her death. She was admitted to Barnes Hospital with signs of congestive heart failure on February 15, 1965. The supine antercposterior overexposed grid roentgenogram of February 23, 1964, (Fig. 6A) shows a large heart and a normal to slightly widened left paravertebral pleural line. Progressive heart failure continued in spite of treatment and a bilateral pleural effusion was noted on the examination of March 16, 1964. Figure 6B, the supine anteroposterior overexposed grid roentgenogram of that ex-



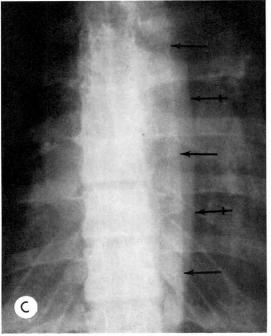


Fig. 6. Case III. (A) A supine anteroposterior overexposed grid roentgenogram of February 23, 1964 demonstrating a normal to slightly widened left paravertebral line  $(\leftarrow)$ . (B) A supine anteroposterior overexposed grid roentgenogram of March 16, 1964 demonstrating widening of the left paravertebral line  $(\leftarrow)$  which has obliterated the aortic line  $(\leftarrow)$ . This is compatible with increasing left free pleural effusion. (C) A supine anteroposterior overexposed grid roentgenogram of April 17, 1964 showing return of the left paravertebral line (←) and a ortic line  $(\leftarrow)$  to the pre-effusion state. Roentgenogram taken following thoracentesis.

amination, shows widening of the left paravertebral pleural line which has obliterated the aortic line. Thoracentesis was performed and a repeat chest roentgenographic examination was made on April 17, 1964. The supine anteroposterior overexposed grid roentgenogram (Fig. 6C) of this examination showed regression of the effusion and return of the left paravertebral pleural line and aortic shadow to the preeffusion state. The patient died suddenly 2 days later of pulmonary embolism.

#### DISCUSSION

It has been adequately documented<sup>8,10</sup> that the paraspinal linear shadow, often seen on the left side and less often seen on the right side of the thoracic spine, is due to the tangential projection of the borders of the lung and adjacent pleural coverings. The descending aorta is demonstrated as an opaque linear shadow lateral to the posteromedial border of the lung on the left side. Numerous disease processes involving tissue medial to the paraspinal pleural line may displace the lung and pleura laterally, thereby widening the paraspinal pleural line at a corresponding anatomic level. 2,8,11

The authors have observed that in free pleural effusions the paravertebral pleural line on adequately penetrated posteroanterior erect roentgenograms will maintain a normal position in relationship to the thoracic spine and descending aorta. However, on the supine overexposed anteroposterior grid roentgenogram the paravertebral line will be widened in the presence of free pleural effusion. This is more often demonstrated on the left side than on the right side.

Widening of the paravertebral pleural line on the supine anteroposterior overexposed grid roentgenogram is proposed as an early diagnostic indicator of free pleural effusion. The supine anteroposterior overexposed grid roentgenogram offers an alternative to the lateral decubitus roentgenogram in demonstrating free pleural effusions, particularly in very ill or elderly patients in whom positioning for the lateral decubitus roentgenogram is often quite difficult.

We concur with the explanation offered by Felson<sup>5</sup> and Fleischner<sup>7</sup> that the widening of the paravertebral pleural line in free effusions, as demonstrated on the supine anteroposterior overexposed grid roentgenogram is probably related to its posterior location where fluid will collect at an early stage and effect lateral displacement of adjacent lung tissue.

#### SUMMARY

Widening of the paraspinal pleural line on the supine anteroposterior overexposed grid roentgenogram of the chest is proposed as an early diagnostic indicator of free pleural effusions. This finding is more often observed on the left than on the right side.

Richard T. Trackler, M.D. The Edward Mallinckrodt Institute of Radiology Washington University 510 South Kingshighway St. Louis, Missouri 63110

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## RADIOPACITY OF XENON UNDER HYPERBARIC CONDITIONS\*

By STEFAN S. WINKLER, M.D., † and JACOB SPIRA, Ph.D.‡ BOSTON, MASSACHUSETTS

XENON, one cf the inert gases with an atomic number (54) in the same range as iodine (53) and barium (56), might be expected to be a good roentgenographic contrast medium with respect to air. Previous studies have demonstrated the faint but definite radiopacity of xenon as compared to air.2,7,10 The contrast has been found too faint to be of any practical use with ordinary roentgenographic techniques.

While it is true that xenon is a faint contrast medium at atmospheric pressure, to our knowledge no previous study has been reported evaluating its radiopacity at higher pressures.

The construction of hyperbaric chambers at several centers makes the roentgenographic use of xenon under hyperbaric conditions a definite possibility.1,3,5

#### METHOD

Xenon,\* supplied in a liter flask, was withdrawn by mercury displacement into 10 cc. plastic (polypropylene) syringes. Twelve syringes were filled to the identical volume, 11 cc. These syringes were placed into a metal frame and the gas inside was compressed by squeezing down on the barrel and locking it into various positions by means of a metal bar traversing the metal frame (Fig. 1). In this way each syringe was roentgenographed at approximately 1, 2.4, 3.3, and 6.1 atmospheres.

Pressures were calculated by measuring the volume of the gas at the different positions of the barrel and applying Boyle's

Room temperature and barometric pressures were recorded and remained essentially constant during the course of the experiment.

Four syringes, each in a metal frame, were placed on a 10×13 inch diagnostic film in a non-screen cassette. The xenon in each of the syringes was at one of the four pressures used in this experiment. In addi tion, an identical syringe filled with water was included on each exposure as a standard for densitometric readings. Each syringe was cycled through each of the four pressures used and roentgenograms were made. In this way, 12 densitometric measurements at each of the four pressures were made using the 12 different samples of gas. All films were exposed at 60 kv., 30 mas., and a target film distance of 40

As a control, air was subjected to the same four pressures, and films were exposed using the same technique and the same standard.

#### RESULTS

Visually, the increase in radiopacity of xenon under increased pressure is very apparent (Fig. 1). From a relatively faint opacity at atmospheric pressure, xenon attains approximately the opacity of water at 3.3 atmospheres and exceeds it at 6.1 atmospheres.

The radiographic density readings for the 12 samples are presented in Table 1. The mean values of the density of xenon, subtracted from the density of water, for the various pressures (last column, Table 1) are presented in Table II, second row. Since the density of xenon at atmospheric pressure is a more convenient baseline, avoiding the cumbersome use of negative numbers, we have converted these figures

<sup>\*</sup> Courtesy, Air Reduction Corporation.

<sup>\*</sup> From The Department of Radiology, Boston University Medical Center, Boston, Massachusetts. † Resident, Department of Radiology, Boston University Medical Center, Boston, Massachusetts. ‡ Assistant Professor of Radiology, Boston University Medical Center, Boston, Massachusetts.

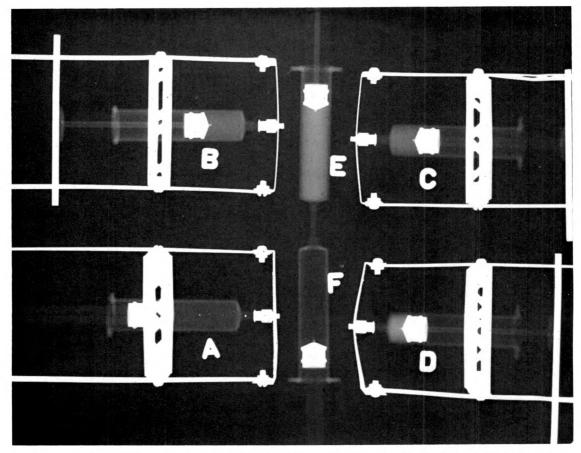


Fig. 1. Xenon at different pressures. (A) 1 atmosphere; (B) 2.4 atmospheres; (C) 3.3 atmospheres; (D) 6.1 atmospheres; (E) water; (F) air at 1 atmosphere.

to the new baseline by simply adding 18 to each value (row 3, Table II). The new values now represent the difference between density of xenon at a pressure of I atmosphere and the density of xenon at the specified higher pressures.

When pressure is plotted against these densitometric readings (Fig. 2), a linear

relationship is approximated.

A linear relationship is predicted since the path-length of xenon is constant for all pressures, and under the conditions of our experiment, the linear absorption coefficient of xenon can be shown to be directly proportional to pressure. Since this holds strictly only for monochromatic radiation, the slight deviation from linearity of our graph for higher pressures also might be expected.

As a control, air was subjected to the same pressures, and neither by visual inspection (Fig. 3) nor densitometric readings (Table III) can an increase in radiopacity with increasing pressure be discerned.

#### DISCUSSION

Because of the theoretic importance of xenon as an anesthetic, a great deal of work has been done on its pharmacology. Xenon as an anesthetic at atmospheric pressure is mild, having the same potency as ethylene.<sup>4</sup> No untoward side effects have been noted in the xenon anesthesias performed on patients and animals.<sup>8</sup>

Of particular interest for our purposes is the work of Pittinger *et al.*<sup>9</sup> who anesthetized monkeys with xenon inside a hyperbaric chamber in order to investigate its an-

Table I

PRESSURE AND RADIOGRAPHIC DENSITY MEASUREMENTS

Film No.	Syringe	Pressure (atmospheres)	Density of Xenon	Density of Water	Density of Water-Density of Xenon
I	A B C D	1 2.4 3.4 6.1	I.12 I.∞ .92 .80	.96	16 04 .04
2	A B C D	2.4 3.2 5.5	.99 .96 .84 I.II	.96	03 0 .12
3	A B C D	3.2 6.1 1 2.4	.97 .90 1.19 1.06	.99	.02 .09 20 07
4	A B C D	6.9 1 2.4 3·3	.80 1.17 1.06 .98	.98	.18 19 08
5	A B C D	1 2.4 3.4 5.2	1.14 1.04 ·97 .81	.97	17 07 0
6	A B C D	2.4 3.2 6.1	1.02 .98 .87 1.18	.99	03 .01 .12 19
7	A B C D	3.2 6.1 1 2.2	1.01 .90 1.22 1.10	1.∞	01 .10 22 10
8	A B C D	6.9 1 3.4 2.9	·75 1.08 ·93 ·90	.92	.17 16 01
9	A B C D	1 3·3 3·7 6.1	1.12 .96 .96 .85	·94	18 02 02 09
Ю	A B C D	2.3 2.3 6.1	1.01 1.02 .85 1.13	-94	07 08 .09 19
II	A B C D	3.4 6.1 1 2.4	.91 .83 1.13 .98	.92	.or .og 21 o6
12	A B C D	I 2 · 4 3 · 4	1.11 1.01 •93	-93	18 08 0

Table II

MEAN VALUES AND THEIR STANDARD DEVIATIONS TAKEN FROM TABLE I

Pressure (atmospheres)	. І	2.4±.1	3.3±.2	6.1±.4
Density of Water-Density of Xenon	18±.02	06±.02	0±.02	.12±.04
Density of Xenon at I Atmosphere  -Density of Xenon at Specified Pressure	0±.02	.12±.02	.18±.02	.30±.04

esthetic properties at increased partial pressures. They found that xenon became increasingly potent with increasing partial pressure. Apnea was induced at a partial pressure of 1,550 mm. Hg and, at 2,250 mm. Hg partial pressure, the monkeys were "areflexic, apneic, completely relaxed." The oxygen tension was kept constant throughout the experiment. All the animals made an uneventful recovery. These experiments show that, at least for some roentgenologic applications of xenon under hyperbaric conditions, one must be prepared to deal with the potent anesthetic effects of xenon at these pressures.

The clinical applications which come to mind are:

1. Bronchography. Essentially, it is envisioned that the subject would inhale deeply and, toward the end of the inspiration (approximately the last 150 cc.), the subject will inhale xenon instead of air or oxygen. The lungs will be filled with air while the bronchi will be filled with xenon. The resulting contrast of densities should outline the bronchial tree. The roentgen-

ray exposure would be made immediately at the end of inspiration to reduce loss of contrast due to diffusion of gas. Only small quantities of xenon would be required and the anesthetic action probably would not be a problem. This technique might be particularly applicable in young infants

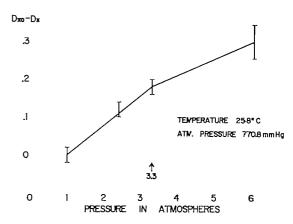


Fig. 2. Arrow indicates pressure at which xenon has same radiopacity as water. Dxo=radiographic density of xenon at pressure of I atmosphere. Dx=radiographic density of xenon at specified higher pressure.

Table III

DENSITOMETRY READINGS FOR AIR CONTROLS

Film No.	Syringe	Pressure (atmospheres)	Density of Air	Density of Water	Density of Water – Density of Air
I	A B C D	1 2.4 3.3 6.1	1.19 1.20 1.18 1.20	.93	26 27 25 27

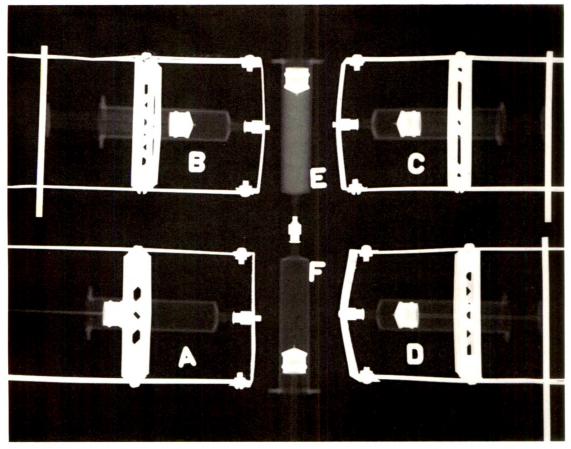


Fig. 3. Air at different pressures. (A) I atmosphere; (B) 2.4 atmospheres; (C) 3.3 atmospheres; (D) 6.1 atmospheres; (E) water; (F) xenon at I atmosphere.

and children, or patients with severe emphysema who might not otherwise tolerate bronchography.

- 2. To study areas of air-trapping and obstruction in the lung. For this, the patient would have to take at least one full inhalation of a gas mixture containing a large percentage of xenon and anesthetic action may or may not be a problem.
- 3. Studies of lung vasculature. Since xenon comes to equilibrium with the blood-stream, its rate of absorption from different areas of the lung might serve as an indicator of adequacy of blood flow to these areas. It might, for example, be another aid in the diagnosis of pulmonary embolism. For this application, one would have to be prepared to anesthetize the patient with xenon at least for a brief period of time.

#### SUMMARY

The radiopacity of xenon at higher pressures is demonstrated. Xenon attains the radiopacity of water between 3 and 4 atmospheres. In this range it might be expected to be a useful contrast medium for studying the lung and bronchial tree. Possible applications with the use of a hyperbaric chamber are discussed.

Stefan S. Winkler, M.D. Department of Radiology New England Medical Center Hospitals 171 Harrison Avenue Boston 11, Massachusetts

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# THE SIGNIFICANCE AND LIMITATIONS OF SKIN THICKENING AS A DIAGNOSTIC SIGN IN MAMMOGRAPHY

By HUGH F. MORRISH, M.D. BALTIMORE, MARYLAND

Mammography has undoubtedly achieved a place in the diagnosis and management of breast disease. We do not intend dispute of this concept but only to demonstrate a need for caution.

It is implied in many recent publications<sup>1,2</sup> that the roentgenogram of the breast can be interpreted with a high index of reliability without knowledge of the clinical history or physical findings. While this is undoubtedly true when reviewing

large numbers of cases, the significance of this reliability is questionable when one is confronted with a truly perplexing case where interpretation of the mammogram may actually influence the clinical management

The intent of the author is to stress a need for caution in attempting mammographic interpretation without knowledge of the clinical history and physical findings as it relates to one roentgenographic crite-

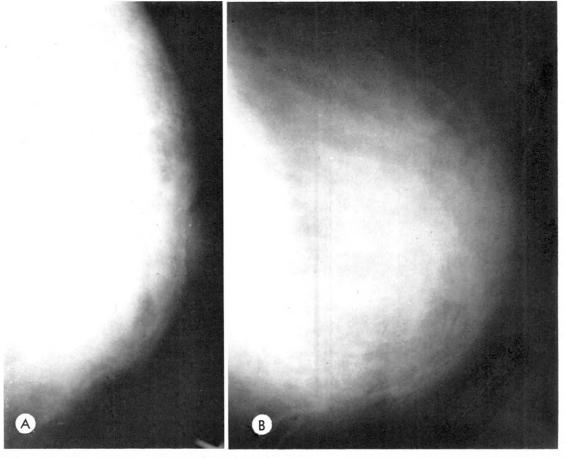


Fig. 1. (A) Inflammatory carcinoma of the breast. (B) Edema secondary to lymphatic obstruction. Previous cobalt 60 therapy for adenocarcinoma of the lung. No evidence of tumor in breast.



Fig. 2. (A) Carcinoma of the breast. Localized skin thickening with underlying breast mass. (B) Localized skin thickening resultant from previous biopsy. No evidence of malignancy.

rion, that of skin thickening.

At the Johns Hopkins Hospital mammographic techniques have been restricted to patients with problems in clinical diagnosis. The mammogram has not been used extensively for routine investigations of breast masses, or as a screening procedure. This case selection profoundly influences any generalizations or conclusions attempted.

Skin thickening, while frequently inter-

preted as secondary evidence of malignancy must be evaluated with care. The varied causes of skin thickening that may be apparent on the roentgenogram can be summarized as follows: 1. localized skin thickening: (a) breast cancer, (b) trauma, (c) biopsy, (d) inflammation (abscess, granuloma), (e) mammary duct ectasia; 2. generalized skin thickening: (a) breast cancer, inflammatory carcinoma of breast, (b) surgery of chest wall or axillary surgery,

(c) dependent edema, congestive heart failure, obesity, (d) ichthyosis and other primary skin disorders, (e) lymphatic obstruction (axillary, intrathoracic), (f) inflammation, (g) following radiation therapy.

In the accompanying mammograms (Fig. 1 through 5) a series of 10 cases, paired because of similar appearance on the roentgenogram is presented. The first member of each pair has surgically proven cancer of the breast. The second member of each pair has similar roentgenographic findings, but secondary to some other process than breast cancer.

#### CONCLUSION

A series of 10 patients demonstrating skin thickening on the mammogram is presented as 5 paired cases. Each pair has similar roentgenographic findings. The first member of each pair shows skin thickening secondary to breast cancer. The second member of each pair shows skin thickening unrelated to breast cancer.

Some of the varied causes of skin thickening are listed.

An attempt is made to demonstrate some limitations of mammographic interpretation as related to skin thickening,

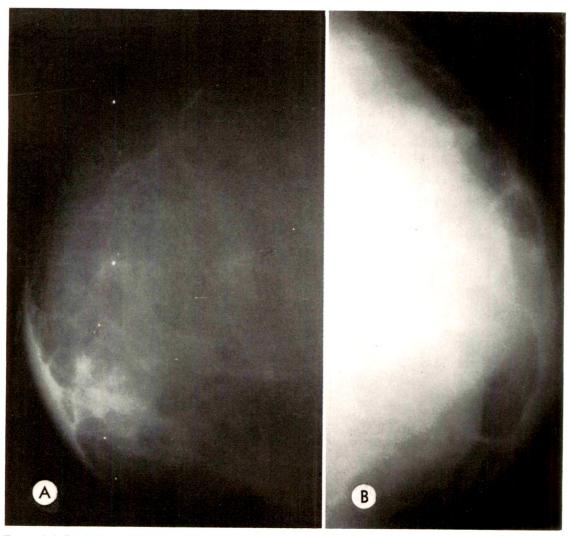


Fig. 3. (A) Carcinoma of the breast. Localized skin thickening with underlying breast mass. (B) No evidence of malignancy in breast. Previous thoracotomy incision transected breast.

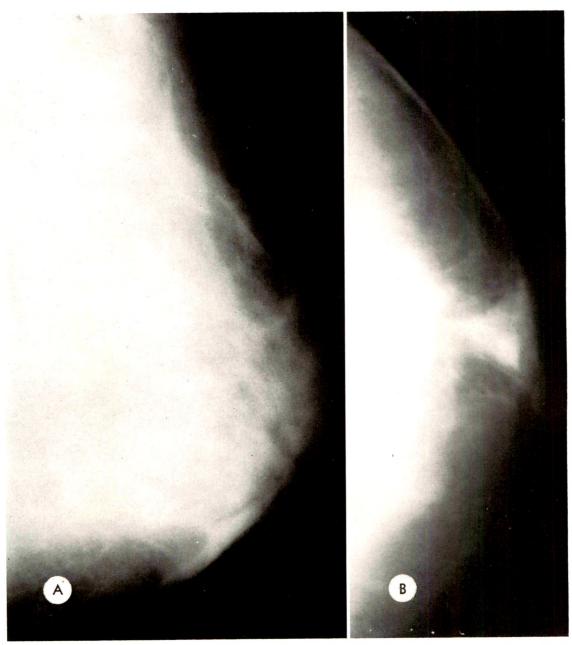


Fig. 4. (A) Carcinoma of the breast. Localized skin thickening with underlying breast mass. (B) Localized skin thickening secondary to previous biopsy. (Subsequent surgery revealed 4 foci of carcinoma in situ, but no frank malignancy which might have been associated with skin thickening.)

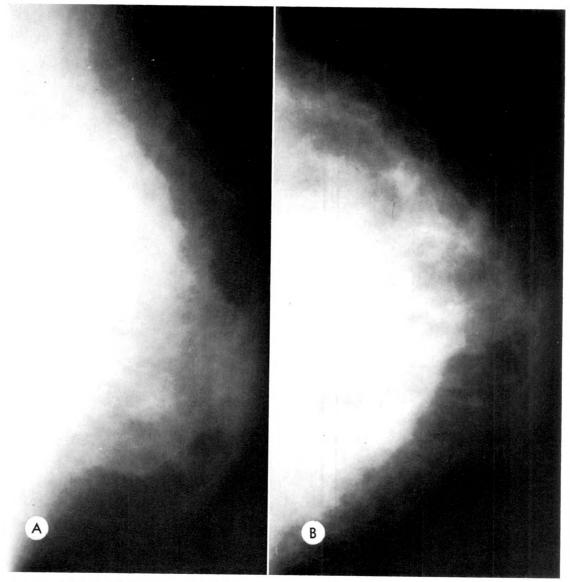


Fig. 5. (A) Inflammatory carcinoma of the breast. (B) Skin thickening secondary to a series of previous biopsies. No evidence of malignancy.

especially when interpretation is undertaken without precise knowledge of clinical history and physical findings.

The Department of Radiology The Johns Hopkins Hospital Baltimore, Maryland 21205

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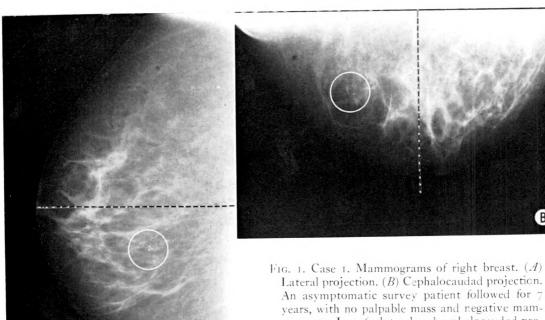
# MAMMOGRAPHIC LOCALIZATION OF UNSUSPECTED BREAST CANCER

By S. M. BERGER, M.D.,\* BARBARA M. CURCIO, R.T.,† J. GERSHONCOHEN, M.D., D.Sc. (Med.), and HAROLD J. ISARD, M.D.§ PHILADELPHIA, PENNSYLVANIA

AT THE Albert Einstein Medical Center, we are approaching our fifteenth year of using mammography as one of the many disciplines employed in the diagnostic x-ray section of this large general hospital. Through 10 of these years, mammography has also been used as a survey project in a group of asymptomatic women who were roentgenographed twice a year. Much has been written and various opinions have been expressed about mammography by us and other groups concerning technique and statistics. There does, however, appear to be a unanimity of opinion that the most important role of mammography is to identify the smaller and nonpalpable lesions of the breast. If mammography can help to reduce the awesome and unchanged statistics in breast carcinoma by detecting earlier, smaller, and hopefully, more localized lesions, attention must be focussed on areas of either nonpalpable infiltration or calcification.

The purpose of this paper is to describe the method of localizing these areas of concern which are unassociated with a clinical mass.

We find it important to function in 3 areas: (1) to direct the surgeon to the correct site for obtaining his biopsy; (2) to



Lateral projection. (B) Cephalocaudad projection. An asymptomatic survey patient followed for 7 years, with no palpable mass and negative mammograms. In 1963 lateral and cephalocaudad projections revealed a clump of small calcific particles in lower outer aspect of right breast suggestive of

an area of intraductal carcinoma. No physical mass was as yet present or palpable.

<sup>\*</sup> Senior Attending in Diagnosis, Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania. † Supervisor, Mammography Section, Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania.
† Director, Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania.
‡ Chairman, Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania.
§ Chairman, Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

decide, while the patient is still under anesthesia, whether the correct site has been dissected and whether the pathologist has been given the correct tissue; and (3) to help the pathologist decide which area should be studied microscopically. This becomes very important in those cases where the gross specimen affords an unremarkable appearance macroscopically.

#### METHOD

A prerequisite for accurate preoperative localization is mammograms which demonstrate the tumor in two projections at right angles to each other. This is accomplished by means of the routine lateral and cephalocaudad projections with the breast supported to the degree necessary to profile nipple and breast tissue, and including all of the mammary gland from chest wall to

nipple (Fig. 1, A and B). One cannot overemphasize the necessity for identifying by lead markers the various quadrants of the breast. We routinely place our markers in the upper aspect of the breast in the lateral projection and in the outer aspect in the cephalocaudad projection. A base line is drawn on the roentgenograms from nipple to chest wall in both projections, and the suspected area is suitably marked (we circle with crayon the suspicious area, including at least an additional perimeter of 0.5 cm. of breast tissue, to allow for minute variations in projection). This procedure localizes the lesion to a specific quadrant of the breast since the lateral projection establishes whether the lesion is above or below the nipple, and the cephalocaudad projection whether it is medial or lateral to the nipple. Since more precise localization

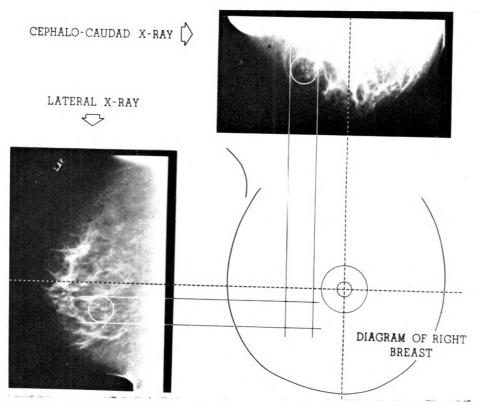


Fig. 2. Case 1. Method of obtaining localization drawing. Lateral and cephalocaudad mammograms with suspected lesion suitably identified adjacent to breast diagram in proper relation to nipple and mid-nipple lines. Superior and inferior borders of suspected area established by erecting lines from lateral mammogram onto drawing at proper levels. Medial and lateral borders of suspected area established by erecting lines from cephalocaudad mammograms onto drawing at proper levels.

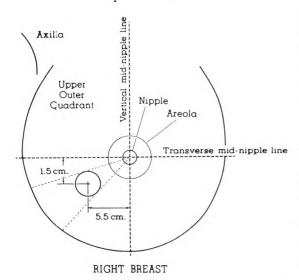


Fig. 3. Case I. Final localization drawing shows location of suspected area, measured from both transverse and vertical mid-nipple lines, nipple, areola, axilla, which is properly identified, and one quadrant of breast, which is labelled. Included with this drawing is the approximate minimum to maximum depth of the lesion from the skin (obtained by measurements made from original roentgenograms) and a note which advises the surgeon to position the patient so that the actual transverse and horizontal mid-nipple lines simulate the perpendicular status shown in the drawing. Maximum accuracy is assured if this procedure is followed.

than merely quadrant localization, is necessary for small nonpalpable lesions and those characterized merely by calcific deposition, the following procedure is utilized. Working over a lightbox and using the mammograms in both projections, we are able to transpose the suspicious area onto a diagram of the breast in exact relation to the nipple, with the exact borders of the lesion clearly indicated (Fig. 2).

The final diagram contains precise measurement of the tumor from each midnipple line (transverse and vertical), the diameter of the areola (measured from the mammograms), one quadrant of the breast clearly labelled, and measurement of the depth of the suspected lesion from the skin (Fig. 3).

This diagram localizes the tumor in the breast with remarkable accuracy, providing

that: (1) the original mammograms are made in true profile; (2) the transposition is done with care and precision; and (3) the patient is positioned at operation so that the transverse and vertical mid-nipple lines on the patient simulate as much as possible the ones shown in the final diagram.

In addition to proper localization of the site for surgery, we act also to assure that the proper area has been removed and to aid the pathologist in deciding which area should be studied microscopically. With both the surgeon and pathologist cooperating, maximum speed of handling is ensured and the removed specimen is sent directly from the operating room to the radiology department.

In the radiology department, the fresh specimen is placed flatly on a piece of waxed paper which has suitable markers affixed to



Fig. 4. Case I. Roentgenogram of biopsy specimen shows the successful removal of the area which contained the suspicious calcific particles. Since the pathologist felt the gross specimen to be negative, a frozen section was not made. Permanent sections of the localized area revealed a tiny intraductal carcinoma.

it. A roentgenogram is taken immediately and while it is being developed, two additional roentgenograms are made. The technique of the specimen roentgenogram varies between 10 and 25 per cent of the original mammography technique. Our average mammographic technique is 200 mas. at 25 kv., with a 14 inch target film distance, fine focal spot, and careful collimation. The specimen roentgenogram is taken at 10–50 mas. at 25 kv., depending on the thickness of the specimen.

The specimen itself remains unchanged in position and is moved from film to film, using the waxed paper as a vehicle. The original roentgenogram is checked immediately and the surgeon is informed as to whether there has been successful removal of the suspected area. The specimen is again

moved via the waxed paper onto a cardboard and covered with damp gauze. Then both specimen and specimen roentgenograms are taken immediately to the pathology laboratory. Since the specimen has been maintained in the exact position used for roentgenography, accurate localization of suspected areas can be made for microscopic study (Fig. 4).

#### REPORT OF CASES

Case I. P.P., a 44 year old asymptomatic survey patient, had returned for examination every 6 months since 1956. In 1963, a mammogram revealed tiny punctate calcifications in the lower outer portion of the right breast, probably present in the examination made 6 months previously. Their pattern, number and size suggested an intraductal malignancy and a guided dissection for biopsy purposes was

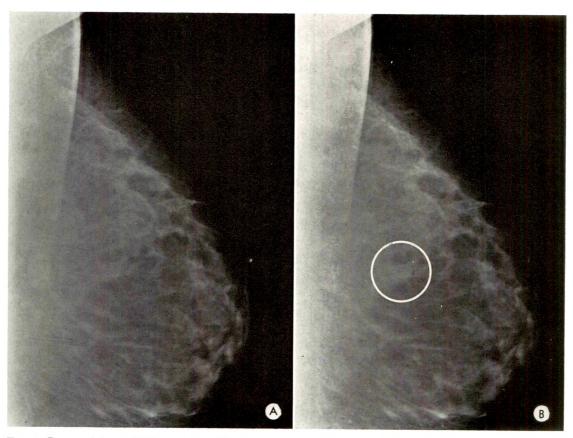


Fig. 5. Case II. (A and B) Two comparative lateral mammograms 3 months apart, in a 45 year old female with localized pain and tenderness, but no definite mass. The minimal increase in size of a dominant roentgen shadow indicated the advisability of an area dissection. Localization technique was performed to guide the surgeon.

recommended. Figure 1, A and B demonstrates the appearance of the particles in the lateral and cephalocaudad projections. No mass was palpable. Figure 3 is the localization drawing sent to the operating room to aid in the dissection of the suspicious area. It localized the area to be dissected in centimeters from the midnipple point, i.e., 1.5 cm. inferior to the transverse nipple line and 5.5 cm. lateral to the vertical nipple line. The area of calcification was situated between 3–5 cm. deep from the skin.

Figure 4 is a roentgenogram of the specimen from which we were able to inform the surgeon that he had removed the correct area. Nothing was palpable in the gross specimen and the pathologist did not perform a frozen section. Permanent sections were obtained in the designated portions of the specimen which proved to contain focal carcinoma *in situ*. No infiltration into the adjacent tissue was present. The axillary lymph nodes were free from metastasis.

This case typifies the ease and certainty with which the radiologist is able to assist both surgeon and pathologist.

Case II. M.G., a 45 year old female, was referred for mammography because of breast pain. No physical mass was palpable and no roentgen evidence of malignancy was identified (Fig. 5A), but because of the type of breast

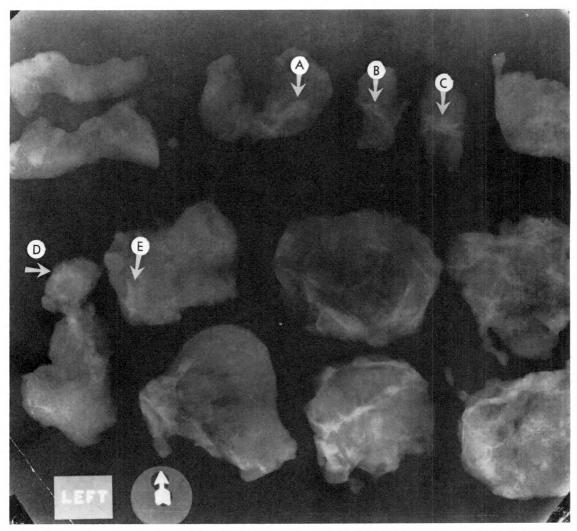


Fig. 6. Case II. Roentgenogram of biopsy specimen. The difficulty of correlating the suspicious shadow in the preoperative mammograms and its counterpart in the biopsy specimen roentgenogram is evident and the radiologist can only suggest several suspicious areas from which permanent sections are to be taken.

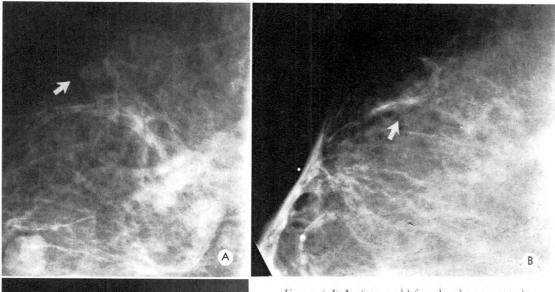




Fig. 7. (A) A 56 year old female who presented with a moderate sized, sharply circumscribed and lobulated, soft tissue shadow at the site of a clinical mass (lower left corner). The roentgen impression was a fibroadenoma. However, a small soft tissue shadow with numerous small calcific particles also suggested a malignancy which was not palpable (arrow). Localization was not done. Surgery revealed the palpable mass to be a fibroadenoma. (B) A study 2 months later showed the suspected carcinoma, which was still not palpable, and an increased number of calcific particles (arrow). Surgery without specific localization was performed. The tissue was negative for cancer. (C) A roentgenogram 2 months later showed again the suspected carcinoma (arrow). At this time a specific area localization was made and a small nonpalpable carcinoma was removed at surgery.

architecture, we suggested using the survey and rechecking in 3 months. On re-examination, the mammograms suggested a small area of irregular soft tissue density (Fig. 5B) which had increased in size and, although still no mass was palpable, a dissection for biopsy purposes was advised. The previously described localization procedure was carried out. When the dissected tissue was palpated, no area of dominance could be found. The specimen was roentgenographed in sliced gross sections (Fig. 6). It was difficult to ascertain whether the original area of dominance seen on the roentgenogram was part of the dissected specimen. We circled the areas of

localized soft tissue irregularity and prominence, and the final pathologic diagnosis was that of an area of sclerosing adenosis.

#### DISCUSSION

When the radiologist observes an area of calcific deposition which definitely requires biopsy, he is able to perform his task in a well defined and accurate manner. On the other hand, occasionally it has been our experience that when the roentgen finding is only that of a suspicious soft tissue shadow unassociated with a clinical mass,

the first obligation of localizing the area for surgical dissection is adequate, but to appreciate or localize the preoperative roentgen shadow and its equivalent on the specimen roentgenogram is difficult. Although the areas on the specimen roentgenogram which are similar to the suspicious shadows on the original mammograms can be indicated, this cannot be done with the same degree of accuracy as in the cases with calcific deposit.

In our experience of over 50 cases in the past 2 years, the soft tissue shadows which represent cancer maintain their dominant, irregular and dense appearance on the specimen roentgenogram. We have also found that benign and inflammatory reactions, such as sclerosing adenosis and plasma cell mastitis, generally account for soft tissue shadows which suggest possible malignancy. In cases where there is evident discrepancy between the pathologist's report and the roentgen opinion, we make every effort to re-examine the patient by mammography I month after surgery. The necessity for this was clearly indicated when we followed an individual who required 3 separate dissections before a malignancy was removed (Fig. 7, A, B and C).

#### CONCLUSION

In view of the unique role that mammography can play in breast cancer detection, particularly in nonpalpable malignancies, it is important that those involved in this discipline be aware of various responsibilities. These include suggesting a preoperative mammographic diagnosis, making an accurate preoperative schematic localization for the surgeon, taking roentgenograms of the biopsy specimen, by which it can be determined whether the dissected area is the area in question, and, finally, making roentgenograms of the specimen so as to localize for the pathologist the sections for microscopic study when there is no area of palpable or grossly visible prominence.

The techniques employed for these purposes at the Albert Einstein Medical Cen-

ter are described in detail.

S. M. Berger, M.D. Division of Radiology Albert Einstein Medical Center York and Tabor Roads Philadelphia, Pennsylvania 19141

We gratefully acknowledge the cooperation of Dr. Irving Young and Dr. Frank Wiedman of the Pathology Department, Albert Einstein Medical Center, Northern Division, Philadelphia, Pennsylvania.



#### LYMPHANGIOGRAPHIC NEEDLE CLAMP

By A. FRANKLIN TURNER, M.D.\*
LOS ANGELES, CALIFORNIA

WITHIN the past few years, a simple practical method has been developed to demonstrate roentgenographically certain areas of the lymphatic system. Although many attempts were made to inject the lymphatic system, no practical method was developed until Kinmonth<sup>1</sup> in 1952 employed the direct intralymphatic injection of water-soluble contrast media into the lower extremities in the study of various forms of edema. Wallace et al.<sup>2</sup> made the method more practical and extended its usefulness to many lymph node groups.

#### TECHNIQUE

The basic technique employed is similar to that described by Wallace et al.<sup>2</sup> During the procedure, lymphatics were frequently inadvertently damaged while attempting to secure the needle in the lymphatic vessel with a ligature. During the past 18 months, a lymphangiographic spring needle clamp has been constructed from a small hair clip\* with a 6.5×30 mm. stainless steel plate spot welded to the lower aspect of the clip (Fig. 1), which has alleviated this difficulty by allowing the needle to be held without the use of ligatures. After the lymphatic vessel has been dissected free of all surrounding tissue, the spring needle

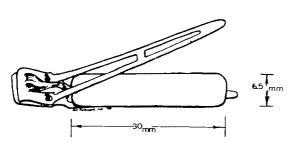


Fig. 1. Lymphangiographic needle clamp in open position, to illustrate component parts.

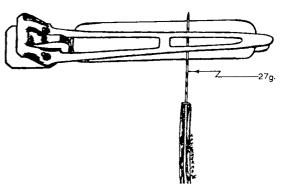


Fig. 2. Lymphangiographic needle clamp in closed position securing needle.

clamp is held open and the lower flattened portion is passed under the lymphatic vessel. The flattened portion of the clamp aids in holding the lymphatic vessel while it is threaded with a 27 gauge lymphangiographic needle, after which the clip is simply closed, securing the needle adequately (Fig. 2). The polyethylene lymphangiographic tubing is then connected to a constant pressure injector.

#### SUMMARY

A simple device for replacing ligatures during lymphangiography is described.

Department of Radiology Los Angeles County General Hospital Los Angeles, California

\* Lady Ellen Klippes (single prong). The Kaynar Company, Los Angeles, California.

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<sup>\*</sup> Assistant Professor of Radiology, University of Southern California School of Medicine, Cardiovascular Radiologist, Los Angeles County General Hospital, Los Angeles, California.

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Representative on the Board of Chancellors of the American College of Radiology; Seymour F. Ochsner. Sixty-seventh Annual Meeting: San Francisco-Hilton Hotel, San Francisco, Calif., September 27-30, 1966.

#### AMERICAN RADIUM SOCIETY

President: Justin J. Stein, Los Angeles, Calif.; President-Elect: Milton Friedman, New York, N. Y.; 1st Vice-President: Manuel Garcia, New Orleans, La.; 2nd Vice-President: Richard J. Jesse, Houston, Tex.; Secretary: John L. Pool, New York, N. Y.; Treasurer: Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colorado 80907.

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Representative on the National Council on Radiation Protection and Measurements: Herbert M. Parker, Richland, Wash., Liaison Member.

Representative on the Board of Chancellors of the American College of Radiology: Charles G. Stetson.

Forty-eighth Annual Meeting—Golden Anniversary of the American Radium Society: Camelback Inn, Phoenix, Ariz., April 13–16, 1966.

#### M E D I T O R I A L S M

# RESPIRATORY DYNAMICS AND CURRENT PATHOLOGIC CONCEPTS OF PULMONARY DISEASE

THE interpretation of roentgen manifestations of pulmonary abnormalities is a difficult and increasingly sophisticated subject. However, it becomes more meaningful and interesting if the abnormalities are analyzed from the standpoints of respiratory dynamics and current pathologic concepts of diseases which affect the lungs. rather than being unduly influenced by the less objective clinical symptoms. Those who understand the roentgenologic manifestations of normal and abnormal pulmonary physiology are able to add much to the clarification of many pulmonary conditions, as has been emphasized by Rigler.<sup>1</sup> Reliable pulmonary function tests<sup>2,3,4</sup> now make it possible for us to determine the exact physiologic and anatomic points at which many pulmonary diseases interfere with normal respiratory function, and this information may be of great help in the interpretation of chest roentgenograms. For example, although a clinical symptom such as dyspnea is quite nonspecific, pulmonary function studies can determine whether it is due to hypoventilation, structural changes in the alveolar walls, or an anatomic shunt which allows mixture of venous and arterial blood.

Probably the most common cause of pulmonary hypoventilation is chronic bronchitis which causes bronchial spasm, partial bronchial obstruction, over-distention of alveoli, diminished blood flow in the alveolar walls, atrophy of the connective tissue in the alveolar walls, and eventually the full-blown picture of obstructive pulmonary emphysema which is accompanied by an increase in the pulmonary arterial pressure, the lung parenchyma containing too little blood and too much gas due to the alveolar over-distention. However, the lungs may also appear "emphysematous" because of vascular diseases associated with diminished pressure and flow in the pulmonary circulation, and it is often difficult on pure radiologic grounds to distinguish between true emphysema and the hypovascularity due to obstruction within the pulmonary arterial circulation. The important clinical investigations and teachings of Fleischner<sup>5</sup> have made us aware of "chronic pulmonary embolism," in which condition there is marked diminution in pulmonary vascularity coincident to multiple small pulmonary emboli which do not produce the radiologic signs usually seen with pulmonary infarctions caused by larger emboli. In such cases, pulmonary function studies will show that the anoxemia which causes the progressive, and often fatal, clinical picture is due to impairment of diffusion or a diminution of the pulmonary capillary blood flow, rather than

<sup>1</sup> RIGLER, L. G. Functional roentgen diagnosis: anatomical image—physiological interpretation. Caldwell Lecture, 1958. Am. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1959, 82, 1—24.

<sup>1</sup> Barden, R. P., and Comroe, J. H., Jr. Roentgenologic evaluation of pulmonary function: correlation with physiologic studies of ventilation. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1956, 75, 668-681.

MED., 1956, 75, 668-681.

BATES, D. V., and CHRISTIE, R. V. Respiratory Function in Disease: an Introduction into the Integrated Study of the Lung. W. B. Saunders Company, Philadelphia, 1964.

<sup>4</sup> COMROE, J. H., JR. Physiology of Respiration: an Introductory Text. Year Book Medical Publishers, Chicago, 1965.

<sup>&</sup>lt;sup>5</sup> FLEISCHNER, F. G. Development of present concepts of pulmonary embolic disease. In: Monograph on Pulmonary Embolic Disease. Edited by A. A. Sasahara and M. Stein. Grune & Stratton, Inc., New York, 1965.

to the hypoventilation or uneven distribution of the gas so characteristic of true emphysema.

Pulmonary arteriography in patients suspected of having an acute pulmonary embolus may show interesting physiologic findings; e.g., a demonstrated pulmonary embolus on one side is sometimes accompanied by poor filling and small caliber of unobstructed pulmonary arterial branches of the opposite lung. Is this due to the so-called "vagovagal reflex" originating on the diseased side? Although the nature of this phenomenon is not yet clear, it may, nevertheless, be an in vivo radiologic method of showing one of the important mechanisms in the cause of sudden death in acute pulmonary embolism; i.e., not only is pulmonary physiology impaired on the side of the embolism, but it may also be seriously impaired in the "normal" lung. These physiologic changes are reversible, as demonstrated by arteriograms following successful pulmonary embolectomy which show normal filling and caliber of these vessels. It would thus seem that future studies of experimentally produced pulmonary infarction by means of more recently developed angiographic techniques, when combined with pharmacologic investigations relating to the humoral mechanisms associated with infarction (role of serotonin, heparin, etc.), will help clarify the pharmacodynamics of pulmonary embolism.

Pathologic studies of the lungs show severe obliterative disease of the smaller branches of the pulmonary arterial system in many conditions in which there is an increase in the intra-arterial pulmonary pressure; e.g., the left-to-right shunts and admixture lesions. These progressive and potentially fatal changes make it urgent that correct diagnosis and treatment of the correctable lesions be made as early as possible. As the peripheral vascular damage progresses, the vessels in periphery of the lungs seem to become less prominent than normal, and the roentgenologic evidence of a discrepancy between a normal or "hy-

povascular" periphery of the lung and the dilated central branches of the pulmonary arteries is sometimes regarded as a poor prognostic sign in patients with left-to-right shunts and mixing defects because it implies advanced obliterative disease of the smaller peripheral pulmonary vessels.

The study of the pulmonary physiology in patients with mitral stenosis continues to be an intriguing subject. The increase in the post-capillary resistance (in the pulmonary venous system) ultimately leads to an increase in the pressure on the arterial side of the capillary bed which initiates the previously described vicious circle of arterial narrowing, further elevation of arterial pressure, etc. It is now possible to see a dynamic radiologic demonstration of increased pulmonary venous pressures during pulmonary arteriography or cine fluorographic studies which show rapid filling of the pulmonary arteries, a delay in their emptying, and slow filling of the pulmonary veins and left atrium.

The presence of pulmonary "B" lines ("Kerley lines") has helped stimulate us to think in terms of altered physiology, because these lines have been shown to be engorged interlobular septal veins or lymphatics caused by increased pressure in the pulmonary venous or lymphatic system. These lines are most commonly seen in mitral stenosis, rarely being seen in congestive failure due to other causes, and are not seen in conditions which cause an increase in the pulmonary intra-arterial pressure; e.g., the left-to-right shunts and admixture lesions. Thus, in the presence of radiologic evidence of heart disease of unknown etiology, these lines have physiologic significance of importance in differential diagnosis. However, if the heart is normal radiologically and clinically, the presence of these lines should stimulate a careful search for diseases which occlude the pulmonary lymphatic system; e.g., pulmonary sarcoidosis, central bronchogenic carcinoma, mediastinal lymphatic involvement due to metastatic disease, etc.

Pathologic studies of the lungs show

that the bronchial arteries provide the arterial blood supply to pulmonary neoplasms and become dilated and tortuous in patients with diseases which diminish pressure in the pulmonary artery.6 In diseases such as bronchiectasis there is often a well developed collateral circulation between the bronchial and pulmonary arterial systems. Indeed, it seems possible under certain circumstances that there may be a reversal of the flow from the bronchial arteries into the pulmonary arteries and thence toward the hilus. Recent angiographic studies have also shown that primary pulmonary neoplasms<sup>7,8</sup> and large metastatic tumors<sup>9</sup> of the lung apparently receive their blood supply from the bronchial arteries. Thus, the further development of arteriographic techniques for studying the bronchial arteries in vivo may be useful in the differential diagnosis of pulmonary diseases in the future.

Careful study of chest roentgenograms often makes it possible to categorize pulmonary diseases as "alveolar" or "interstitial" in nature. The alveolar diseases in general are more prone to produce poorly defined fluffy-appearing water-density lesions, whereas the interstitial diseases produce a more stringy reticulated appearance, suggesting involvement of the peribronchial tissues and lymphatics. Sarcoidosis, pneumonias, pulmonary infarction, pulmonary edema, pulmonary alveolar proteinosis, etc., are but a few examples of the "alveolar" diseases, whereas diseases which produce chronic interstitial pulmonary fibrosis (Hamman-Rich syndrome) or engorgement of the pulmonary lymphatic system (eosinophilic granuloma, sarcoid) present a picture described as "interstitial" or reticulated. Thus, if we strive to improve

<sup>6</sup> LIEBOW, A. A., HALES, M. R., and BLOOMER, W. E. Relation of bronchial to pulmonary vascular tree. In: Pulmonary Circulation. Edited by W. R. Adams and I. Veith. Grune & Stratton, Inc., New York, 1959, pp. 79-08.

Inc., New York, 1959, pp. 79-98.

<sup>7</sup> Newton, T. H., and Precer, L. Selective bronchial arteriography. Radiology, 1965, δ4, 1043-1061.

ography. Radiology, 1965, 84, 1043-1051.

NIAMONTE, M., Jr. Selective bronchial arteriography in man: preliminary report. Radiology, 1964, 83, 830-839.

NOONAN, C. D., MARGULIS, A. R., and WRIGHT, R. Bronchial

our ability to analyze and categorize pulmonary diseases as either vascular, alveolar, interstitial or mixed, it is frequently possible to get "in the ball park" from a diagnostic standpoint, rather than resorting to diagnostic nihilism on the one hand, or a useless guessing game on the other.

The investigation of bronchial dynamics has been stimulated by the advent of cinebronchography and more thorough bronchographic spot-filming techniques. As a result, interesting new concepts of the etiologic mechanisms involved in the production of bronchiectasis are now being investigated. Frazer et al. 10 have shown that a lobar bronchus proximal to ectatic segmental and subsegmental bronchi may collapse to an abnormal degree during expiration with a resultant increase in the intrabronchial expiratory pressure in the more peripheral ectatic bronchi. It is postulated that this collapse is due to softening of the wall of the lobar bronchus subsequent to chronic bronchitis. Whether or not this is an etiologic factor in the production of bronchiectasis in the more distally located bronchi will probably be clarified as these interesting studies continue.

Thorough bronchographic studies show that severe pulmonary emphysema is almost always accompanied by many bronchographic manifestations of chronic bronchitis; e.g., bronchial spasm, excessive secretions, dilated mucosal glands, bronchiolectasis, etc. Thus we are now becoming familiar with a meaningful etiologic concept of emphysema; i.e., the overwhelming majority of patients suffering from far advanced emphysema are heavy cigarette smokers who have severe clinical and bronchographic evidence of chronic bronchitis. Many of us are now convinced that heavy cigarette smoking and the subsequent bronchitis with the resultant chronic bronchial spasticity is the single most important etiologic mechanism in the production of obstructive emphysema.

<sup>10</sup> Fraser, R. G., Macklem, P. T., and Brown, W. G. Airwry dynamics in bronchiectasis: combined cinefluorographic-manometric study. Am. J. Roentoenol., Rad. Therapy & Nuclear Med., 1965, 93, 821–835.

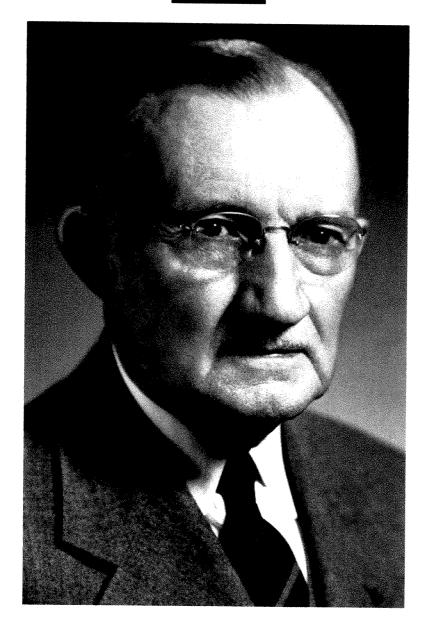
NOONAN, C. D., MARGULIS, A. R., and WRIGHT, R. Bronchial arterial patterns in pulmonary metastasis. *Radiology*, 1965, 84, 1033–1042.

Our improved understanding of respiratory dynamics and pathology now makes it possible to approach chest roentgen diagnosis on a more objective basis. Although the clinical symptoms are of great interest to any physician, including the radiologist, they are so frequently nonspecific and misleading that is it often hazardous to be unduly influenced by them in making a roentgenologic diagnosis. It is far better to try to make an objective roentgenologic attempt to categorize pulmonary diseases as vascular, alveolar, interstitial, or mixed in nature. The further correlation of the information relating to respiratory dynamics with the objective roentgenologic evidence of disordered pulmonary physiology and pathologic anatomy then becomes highly rewarding to radiologists, their referring colleagues, and their patients. Obviously, the radiologist must try to make his diagnosis primarily on the basis of what he sees on the roentgenogram. However, there is so much to see on the roentgenograms!

Sidney W. Nelson, M.D. President, Association of University Radiologists

Professor and Chairman Department of Radiology The Ohio State University Hospital 410 West 10th Avenue Columbus 1, Ohio





OTTO H. FOERSTER, M.D. 1875-1965

A FATAL coronary occlusion ended a long and distinguished medical career of one of Milwaukee's oldest physicains on July 18, 1965, with the death of Dr. Otto H. Foerster, at Columbia Hospital.

Hearing first of the "new ray" while a medical student at the University of Penn-

sylvania in 1896, and graduating in medicine in 1898, Dr. Foerster promptly enlisted with the 4th Wisconsin Volunteer Infantry as a steward, and served during the Spanish-American War period, until his regiment was mustered out of service.

He served a term as resident physician at

Howard Hospital, Philadelphia (no longer in existence), followed by work in medicine and dermatology in the Polyclinic (now the Graduate Hospital of Philadelphia). Later he went to Europe and studied for 18 months at the Allegmeines Krankenhaus in Vienna, then returned to Philadelphia as a research associate at the Pepper Laboratory of the University Hospital, and as clinical assistant in dermatology at the Polyclinic and other Philadelphia hospitals.

He returned to his home city of Milwaukee in October 1902, and soon limited his practice to dermatology and radiotherapy. He was the first physician in Milwaukee to apply radium therapeutically in 1902, about the same time that another dermatologist, Dr. Louis Frank, first used x-rays therapeutically.

In 1907, at the age of 32, he married Miss Louise Leidersdorf, the union continuing happily throughout the remaining 58 years of a very active professional life.

Dr. Foerster was the first Professor of Dermatology at the University of Wisconsin Medical School in Madison, and was an organizer and associate editor of the Wisconsin Medical Journal which began publication in 1903. In 1909 he helped organize Columbia Hospital in Milwaukee and for a period of 10 years served as its Chief of Staff.

In 1924, his younger brother, Dr. Harry R. Foerster, following graduate training in dermatology with Dr. George McKee of New York City, came to Milwaukee and together the brothers practiced dermatology for 40 years.

In addition to memberships in local, state, and national medical and dermatological societies in this country, he was a foreign member of the French Dermatologic Society. He was the first non-resident member of the Chicago Dermatological Society.

He served as President of the Milwaukee Academy of Medicine, The Chicago Dermatological Society, and the American Dermatological Association (of the latter both in 1913 and again in 1937). In 1919, he was Chairman of the Section on Dermatology of the American Medical Association. He was one of several Honorary Vice Presidents of the International Congress of Dermatology held at Washington, D.C., in 1962.

He was a Charter Member of the Milwaukee Roentgen Ray Society, organized in 1923 and in 1963 at the 40th anniversary meeting of the Society was declared an Honorary Member of that Society.

He was one of 9 physicians to be elected to the American Roentgen Ray Society in 1910, together with such other medical stalwarts as James T. Case, Walter Dodd, George Grier, Leon T. Le Wald and the several others constituting the select group.

He was author of many articles in his field of specialized practice, and was a contributor to Abt's Pediatrics and Blumer's Therapeutics.

Dr. Foerster did not have many hobbies or outside interests. Hence, even in the last several years of his life, it was not surprising to see him moving cautiously through downtown traffic on his way to and from his office in the new Marine Plaza Building.

He was a Captain in the Medical Corps, U. S. Army, during World War I, serving at Camps Greenleaf and Gordon in Georgia.

He was a member of the Military Order of Foreign Wars, of Phi Gamma Delta Social Fraternity, and Alpha Mu Pi Omega Medical Fraternity.

Survivors of the immediate family include the widow, one daughter, Frances, wife of Dr. Dean Echols, of Tulane Medical School and the Ochsner Clinic in New Orleans, a son Frederick, an internist practicing in Milwaukee, and the younger brother Dr. Harry Foerster.

J. Edwin Habbe, M.D.

231 W. Michigan Street Milwaukee, Wisconsin 53203

#### **NEWS ITEMS**

### THE AMERICAN COLLEGE OF RADIOLOGY

The Forty-second Annual Meeting of the American College of Radiology was held at the Drake Hotel, Chicago, Illinois, February 1 to 5, 1966.

The following officers were elected: President, Jackson E. Livesay, M.D., Flint, Michigan; Vice-President, Laurence L. Robbins, M.D., Boston, Massachusetts; Secretary-Treasurer, Fay H. Squire, M.D., Chicago, Illinois (re-elected); Chairman, Board of Chancellors, J. E. Miller, M.D., Dallas, Texas; and Vice-Chairman, Board of Chancellors, Joseph D. Calhoun, M.D., Little Rock, Arkansas.

The Convocation Ceremonies were held on February 4, 1966 in the Gold Coast Room, with Dr. Wallace D. Buchanan, President of the American College of Radiology, presiding. The degree of Fellow of the College was conferred on 43 candidates and the degree of Associate Fellow on 2 candidates who had been approved by the Board of Chancellors and elected to fellowship by vote of the Fellows. The degree of Honorary Fellow was bestowed on Carl Solve Halvard Welin, Malmö, Sweden; and in absentia on James W. D. Bull, London, England; Erik Lindgren, Stockholm Sweden; Pierre Porcher, Paris, France; David W. Smithers, London, England; and Sir Brian Windeyer, London, England.

Gold Medals, the highest award of The American College of Radiology, for "distinguished and extra-ordinary service" were presented by President Buchanan assisted by the new President, Dr. Livesay, to Dr. Thomas B. Bond, Dr. Augustín Castellanos, and Dr. William LeRoy Thompson in a most impressive accolade ceremony.

The Forty-third Annual Meeting of the College will be held at the Beverly Hilton Hotel, Los Angeles, California, January 31 to February 4, 1967.

#### DR. LAURISTON S. TAYLOR AND DR. GORDON M. KLINE HONORED

Two world-renowned scientists have received the Edward B. Rosa award presented annually by the National Bureau of Standards, U. S. Department of Commerce, for outstanding achievement in the development of standards of practice. Dr. Lauriston S. Taylor, a leading authority for nearly four decades on the protection of human beings from radiation, and Dr. Gordon M. Kline, internationally known for his research on the physics and chemistry of plastics, accepted the awards from Dr. Allen V. Astin, NBS Director, at a special staff meeting.

The Rosa award, named after Dr. Edward B. Rosa, a member of the Bureau's original staff and its first Chief Physicist, was established in 1964. Throughout his career, Dr. Rosa was very active in the development of standards of practice and made important original contributions to fundamental standards in the fields of electricity and photometry. The award recognizes outstanding accomplishments in the field of standards of practice—the standards by which industry judges its operations, its production processes, and the quality of its products. These standards are almost always in the form of voluntary industry agreements; the National Bureau of Standards serves industry by acting as technical advisor, and, where necessary, as administrative coordinator in the development of these standards. Because of this, the technical and committee work on standards of practice is exceedingly demanding, requiring the highest degree of technical competence and administrative skill.

Dr. Taylor was cited for "outstanding leadership and significant individual contributions in the development of national and international standards for radiation protection." Dr. Kline was cited for "out-

standing leadership and significant individual contributions in the development of national and international standards in the field of plastics."

#### EIGHTEENTH ANNUAL JOSEPH AND SAMUEL FREEDMAN LECTURES

On Saturday and Sunday, April 16 and 17, 1966, Dr. Edward B. Singleton, Director of Radiology, St. Luke's and Texas Children's Hospital, Houston, Texas, will deliver the Eighteenth Annual Joseph and Samuel Freedman Lectures in Diagnostic Radiology at the University of Cincinnati College of Medicine.

Radiologists desiring to attend are requested to write Dr. Benjamin Felson, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio 45221, for further details.

#### SOUTHERN RADIOLOGICAL CONFERENCE

At the Tenth Annual meeting of the Southern Radiological Conference at the Grand Hotel, Point Clear, Alabama, the following new officers were elected: Chairman, Everette H. Schultz, Jr., M.D., Chapel Hill, North Carolina; Vice-Chairman, Byron G. Brogden, M.D., Baltimore, Maryland; and Secretary-Treasurer, Marshall Eskridge, M.D., Mobile Infirmary, P. O. Box 4097, Mobile, Alabama.

The Eleventh Annual meeting will be held at the Grand Hotel, Point Clear, Alabama, January 28–30, 1967.

### POSTGRADUATE COURSE IN RADIOLOGY OF THE GASTROINTESTINAL TRACT

A postgraduate course sponsored by Columbia University College of Physicians & Surgeons, in "Radiology of the Gastro-intestinal Tract" will be given May 5-7, 1966.

Emphasis will be placed on some of the basic and newer aspects of gastrointestinal radiology. Included in the program will be a clinical evaluation of selective abdominal angiography in the detection of intestinal disease, technical considerations involved in the more recent modifications of the gastrointestinal examination, as well as specific topics concerning both pediatric and adult diagnostic problems.

Further information concerning registration may be obtained through the offices of Melvin D. Yahr, M.D., Assistant Dean, College of Physicians & Surgeons, 630 West 168th Street, New York, New York 10032.

#### PUBLIC HEALTH X-RAY CONFERENCE

The Department of Radiology, University of Miami and the Florida State Board of Health with the cooperation of the U. S. Public Health Service, Division of Radiological Health, announce a Public Health Conference on the Use of X-Rays in Medicine and Industry, to be held at the University of Miami, Coral Gables, Florida, April 13–15, 1966.

Guest speakers will be experts of national and international prominence in the x-ray field. The faculty includes: Donald R. Chadwick, M.D., Washington, D. C.; Richard H. Chamberlain, M.D., Philadelphia, Pennsylvania; H. B. Cottrell, M.D., Atlanta, Georgia; Maxwell Dauer, Ph.D., Miami, Florida; James W. Miller, D.D.S., Rockville, Maryland; Charles B. Minnich, BSEE, Orlando, Florida; Karl Z. Morgan, Ph.D., Oak Ridge, Tennessee; R. T. Murphree, Ph.D., Oak Ridge, Tennessee; Raymond E. Parks, M.D., Miami, Florida; Wilson T. Sowder, M.D., M.P.H., Jacksonville, Florida; Lauriston S. Taylor, D.Sc., Washington, D. C.; James G. Terrill, Jr., BSCE, M. Biorad., Washington, D. C.; E. Dale Trout, D.Sc., Corvallis, Oregon; Heinz S. Weens, M.D., Atlanta, Georgia; Edwin G. Williams, M.D., Jacksonville, Florida; and Arthur H. Wuehrmann, D.M.D., Birmingham. Alabama.

The program will consist of lectures and panel discussions and it will include information on new developments on x-ray equipment, design and procedures to minimize exposure. The purpose of the confer-

ence is to more clearly define the contribution of x-rays to population radiation exposure.

For additional information please contact: Maxwell Dauer, Ph.D., Department of Radiology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Florida.

#### SYMPOSIUM ON SOLID STATE AND CHEMICAL RADIATION DOSIMETRY IN MEDICINE AND BIOLOGY

This symposium will be held in Vienna, Austria, October 3-7, 1966 under the auspices of the International Atomic Energy Agency (IAEA).

The Symposium will deal with the dosimetric systems based on condensed state phenomena. All aspects of these systems relevant to their suitability for absorbed dose determination in biology and medicine will be covered.

Requests to present papers or to participate must be submitted through the appropriate national authorities responsible for atomic energy matters, from whom detailed information and application forms can be obtained.

The Scientific Secretaries are Dr. H. Eisenlohr and Dr. R. Loevinger, Division of Isotopes, IAEA, Vienna.

Abstracts of papers for consideration by the Scientific Secretariat must be received in Vienna by May 1, 1966.

#### PACIFIC NORTHWEST RADIO-LOGICAL SOCIETY

The Annual Meeting of the Pacific Northwest Radiological Society will take place at the Empress Hotel in Victoria, British Columbia, Canada, on May 6, 7 and 8, 1966.

The guest speakers will be Robert G. Fraser, M.D., of McGill University, Montreal, and Harold G. Jacobson, M.D., of New York University, New York.

For additional information please contact Dr. Willis J. Taylor, Secretary-Treasurer, 1118 Ninth Avenue, Seattle, Washington 98101.

#### MEDICAL PHYSICS SYMPOSIUM, UNIVERSITY OF WISCONSIN

A symposium on the applications of physics to medicine will be held June 9, 10 and 11 at the University of Wisconsin, Madison, Wisconsin. The symposium is jointly sponsored by the American Association of Physicists in Medicine and the University of Wisconsin Medical Center.

The program will consist of invited papers on selected topics or contributed papers in medical physics. One half-day session will be devoted to invited papers on the physics of bones, and a second half-day session will consist of invited papers on radium leakage, body composition, physics of the ear and ocular effects of laser radiation. There will be two sessions of contributed papers, one of which will be devoted to general papers and the other to papers dealing with thermoluminescence dosimetry.

Two hundred word abstracts for contributed papers are due by May 1.

Further information and advance registration forms are available from: J. R. Cameron, Department of Radiology, University of Wisconsin, Madison, Wisconsin 53706.



#### BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

RESPONSE OF THE NERVOUS SYSTEM TO IONIZING RADIATION. Second International Symposium held at the University of California, Los Angeles. Edited by Thomas J. Haley, Ph.D., Laboratory of Nuclear Medicine and Radiation Biology, University of California, Los Angeles, Calif.; and Ray S. Snider, Ph.D., School of Medicine and Dentistry, University of Rochester, Rochester, N. Y. Cloth. Pp. 768, with 392 illustrations. Price, \$18.50. Little, Brown and Company, Mass. 02106, 1964.

This symposium was a multi-disciplinary conference on the pathologic, chemical, functional and behavioral responses of the nervous system to ionizing radiation by some 109 neuropathologists, radiologists, radiobiologists, neurologists, neurosurgeons, neurophysiologists, biochemists and psychologists. The 40 reports in this volume contain a great amount of information and criticism in many different fields. To adequately discuss each of the 40 reports a specialist in that field would be necessary and for this reason, only general comments can be given.

The reaction of the nervous system at the subcellular and cytochemical levels is described as well as the gross and microscopic changes due to radiation. Pharmacologic and electrophysiologic responses are considered as far as they are presently known. The last group of papers deals with the effects of radiation on conditioned reflexes, on the autonomic nervous system, on behavioral development and on radiation as a perceptual and aversive stimulus. The references for each report are lengthy and could serve as basic bibliographies of each topic dealt with.

This text is of interest to persons in the fields of radiobiology, neuropathology, neurology, neurosurgery, neuroradiology, neurophysiology and biochemistry. It could serve as an authoritative reference to clinical workers in these fields as well as a source of inspiration for research. The laboratory scientist will need it as a summary in fields closely related to his chosen interest and as a source of ideas that might be applicable to his specialty.

The volume has been divided into the following 5 sections: Part I. Cytological Changes after Radiation of the Nervous System; Part II. Radiation-induced Changes in the Peripheral Nervous System and Spinal Cord; Part III. Effects of Radiation on Brain Biochemistry; Part IV. Radiation-induced Functional Changes in the Central Nervous System; and Part V. Effects of Radiation on Behavior.

The publisher has produced a handsome volume of first class quality. The print is of good size. The photomicrographs are of good size and excellent quality. The format is pleasing with no crowding of the material. Indexing such a volume is always a problem. A complete index would be huge. The fifteen page index that is supplied is probably adequate.

D. L. McRAE, M.D.

THE ESSENTIALS OF ROENTGEN INTERPRETATION. Second edition. By Lester W. Paul, M.D., Professor of Radiology, The University of Wisconsin Medical School; and John H. Juhl, M.D., Professor of Radiology, Chairman of Department of Radiology, The University of Wisconsin Medical School. Cloth. Pp. 902, with 1,263 illustrations. Price, \$25.00. Hoeber Medical Division, Harper & Row, Publishers, 49 E. 33rd Street, New York, N. Y., 1965.

The second edition of this book fulfills in an exemplary manner the objective for which it was designed, namely, a text to bridge the gap between the elementary text and the multiple-volume reference work. This is accomplished by necessarily brief discussions of roentgen diagnosis of the common, and some of the unusual, conditions and diseases with positive roentgen findings.

The basic format of the first edition has not been altered, but the text material has been revised in some chapters and discussions and illustrations of a large number of additional pathologic states have been included. The book makes no attempt at encyclopedic coverage or inclusion of much of the recent work in the field of cardiovascular or neurologic radiology. Sixty-

three additional pages of text have been added as well as 128 new illustrations. Some of the illustrations of the first edition have been replaced. New references have been added with the inclusion of discussions of additional diseases.

The illustrations are not of sparkling quality but adequately demonstrate the pathology and their position in relationship to the text material makes for easy reading.

To summarize, this is an excellent general text on the subject of diagnostic radiology which will continue to be useful to all physicians and students involved in roentgen diagnosis.

Theodore E. Keats, M.D.

#### **BOOKS RECEIVED**

RADIOISOTOPE TECHNIQUES IN THE STUDY OF PROTEIN METABOLISM. Findings of a panel on radioisotope techniques in the study of protein metabolism, held in Vienna, June 1-5, 1964. Technical Reports Series No. 45. Paper. Pp. 258. Price, \$5.50. International Atomic Energy Agency, Vienna, 1965. Distributed by International Publications Inc., 317 East 34th Street, New York 16, N. Y., 1965.

Atlas of Radiation Dose Distributions. Volume I. Single-Field Isodose Charts. Compiled by E. W. Webster, Department of Radiology, Massachusetts General Hospital, Boston; and K. C. Tsien, of the International Atomic Energy Agency. Cloth. Pp. 55, and 155 charts. Price, \$15.00. International Atomic Energy Agency, Vienna, 1965. Distributed by International Publications, Inc., 317 East 34th Street, New York 16, N. Y., 1965.

IONIZING RADIATIONS. By J. S. Strettan, M.A., M.Sc., Head of Physics Department, Lady Margaret School. Paper. Pp. 178, with many illustrations. Price, \$3.50. Pergamon Press, Headington Hill Hall, Oxford, England, 1965.

L'APLASIE MYELO-LYMPHOIDE DE L'IRRADIATION TOTALE: EXPRESSION, APPLICATIONS, TRAITE-MENT. By Georges Mathé, Professeur agrégé de cancérologie à la Faculté, Médecin des Hôpitaux; Directeur de l'Institut de Cancérologie et d'Immunogén étique (Villejuif); Chef du Service d'Hématologie de l'Institut Gustave-Roussy; Jean-Louis Amiel, Chef de Clinique à la Faculté; Directeur-adjoint de l'Institut de Cancérologie et d'Immunogénétique; Assistant du Service d'Hématologie de l'Institut Gustave-Roussy; and Léon Schwarzenberg, Hémobiologiste des Hôpitaux; Consultant à l'Institut de Cancérologie et d'Immunogénétique; Assistant f. f. du Service d'Hématologie de l'Institut Gustave-Roussy. Cloth. Pp. 245, with 117 figures. Price \$12.00. Gauthier-Villars & Cie, Quai des Grands-Augustins, 55, Paris, France, 1965.

Gastroenterologische Isotopendiagnostik. By Dr. med. habil. Oskar Andrysek, C.Sc., Dozent am Institut für Biophysik und Nuklearmedizin der Karls-Universität Prag; and Dr. med. habil. Hans Berndt, Chefarzt an der Robert Rössle-Klinik, Berlin-Buch. Paper. Pp. 241, with 101 figures. Price, Engl. Broschur 44,80 MDN. Veb. Verlag Volk und Gesundheit, Berlin, 1965.

DISEASES OF ANCIENT MEN (BONES OF THE MEN OF VARIOUS EPOCHS—NORMAL AND PATHOLOGICAL CHANGES). In Russian. By D. G. Rokhlin. Cloth. Pp. 303, with many illustrations. Publishing House "Nauka," Moscow, USSR, 1965.

Lehrbuch der Röntgendiagnostik. In fünf Bänden. Edited by Prof. Dr. med. H. R. Schinz, Zürich; Prof. Dr. med. W. E. Baensch, Washington; Prof. Dr. med. W. Frommhold, Berlin; Prof. Dr. med. R. Glauner, Stuttgart; Prof. Dr. med. E. Uehlinger, Zürich; and Prof. Dr. med. J. Wellauer, Zürich. Volume I. Allgemeine Grundlagen und Methoden. Cloth. Pp. 576, with 683 illustrations. Price, Halbleder DM 198,-. Georg Thieme Verlag, Stuttgart, Germany. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16. N. Y., 1966.

16, N. Y., 1965.

Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals. Twentieth edition. Albert B. Miller, General Manager. Cloth. Pp. 1131. Price, \$7.50. Physicians' Desk Reference, Medical Economics, Inc., Oradell, N. J., 1966.

Trattato di Radiodiagnostica. Volume I, in two parts. Edited by Luigi Turano, Direttore dell'Istituto di Radiologia dell'Universitá di Roma. Cloth. Pp., Tomo primo, 612, with 410 figures; and Tomo secondo, 503, with 419 figures. Price, Volume I, Tomo I and 2, L.30,000. Unione Tipografico, Editrice Torinese, Corso Raffaello 28, Torino, Italy, 1965.



## ABSTRACTS OF RADIOLOGICAL LITERATURE

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#### ROENTGEN DIAGNOSIS

#### NERVOUS SYSTEM

Howard, F. M., and Shafer, S. J. Injuries to the clavicle with neurovascular complications: a study of fourteen cases. J. Bone & Joint Surg., Oct., 1965, 47-A, 1335-1346. (Address: Dr. Howard, 7939 South Western Avenue, Chicago, Ill.)

Although neurovascular disturbances related to injuries of the clavicle are uncommon, this complication may occur when any injury or deformity causes encroachment on the space between the clavicle and first rib.

Mechanical compression or angulation of the subclavian vessels, the brachial plexus, or the carotid artery are the common mechanisms responsible for neurovascular involvement associated with clavicular injuries.

It is the purpose of the authors to report on 14 cases of neurovascular complications associated with injuries to the clavicle.

Seven patients were treated by the authors themselves or were examined personally at follow-up. The remaining 7 were followed by the surgeons who treated them originally. The shortest follow-up was 9 months; the longest was 4 years after the end of treatment.

Résumés of 14 cases are briefly summarized in tabular form.

Evidence of injury to the brachial plexus may be apparent at the time of fracture of the clavicle as the result of pressure from a displaced bone fragment or of axonotmesis consequent to stretching of the brachial plexus. Careful evaluation of the direction and magnitude of the force causing the injury may help to make the correct diagnosis.

Massive callus formation about a healed fracture can also obstruct the thoracic outlet.

Sagging of the shoulders, weakness or loss of tone in the suspensory muscles of the shoulder girdle (the trapezius, levator scapulae, or rhomboids), or sustained downward and backward displacement of the shoulders may also cause neurovascular compression.

Persistent abduction of the arm, such as occurs in ceiling painters, automobile mechanics, and persons who sleep with an arm elevated over the head, likewise may cause neurovascular compression.

Congenital anomalies, such as a bifid clavicle or a straight clavicle with no medial and anterior angulation, may narrow the costoclavicular space and lead to neurovascular compression.

From the series reported by the authors, it appears that neurovascular compressions associated with injuries to the clavicle fall into 2 general groups: (1) obstruction of the carotid artery at the medial end of the clavicle causing symptoms of syncope; and (2) compression of the subclavian vessels or brachial

plexus between the clavicle and first rib. In addition to compression, there may be thrombosis of the subclavian artery and vein, aneurysm of the subclavian artery, and subclavian arteriovenous fistula.

Neurovascular complications associated with acute fractures of the clavicle should be recognized promptly. Early reduction and adequate immobilization of the fracture are usually sufficient treatment.

With injury to the brachial plexus and fracture of the clavicle, it is, of course, essential to determine whether the defect in nerve function is caused by compression or stretching of the plexus. The history, physical findings, electromyographic studies, and the strength-duration curve of involved muscles help to establish the diagnosis.

A battery of tests and maneuvers should be applied, including the Adson test, the costoclavicular maneuver, the attention test, downward traction on the upper extremity, and the hyperabduction test. Significant pulse changes are associated with aggravation of the patient's symptoms.

Open reduction and internal fixation of a recent fracture that is not severely comminuted is a satisfactory way to relieve neurovascular compression. Early open reduction of a posterior dislocation of the medial end of the clavicle is indicated to relieve pressure on the common carotid artery.

With long-standing neurovascular compression, exploration of the brachial plexus with lysis of adhesions may be helpful. Similarly, exploration of the subclavian artery to eliminate compression by scar tissue should be considered if resection of the clavicle does not restore the radial pulse.

Resection of the clavicle would appear to be the treatment of choice to relieve neurovascular compression when massive callus formation is present after fracture, or when internal fixation and bonegrafting of a pseudarthrosis is impractical because of comminution. Resection is also indicated when there is malunion with severe deformity.

If a posterior dislocation of the sternoclavicular joint cannot be reduced, the medial two-thirds of the clavicle can be resected. The middle third or inner two-thirds of the clavicle may also be resected to relieve neurovascular compression caused by malunion of comminuted fractures of the middle third.

It should be noted that if regeneration of the clavicle after resection is undesirable, the resection should be extraperiosteal.

In the event that resection is necessary in a child, the clavicle should be removed subperiosteally since regeneration and continued growth would be desirable under these circumstances.—Stephen N. Tager, M.D.

FISHER, ROBERT L. An experimental evaluation of pantopaque and other recently developed myelographic contrast media. *Radiology*, Sept., 1965, 85, 537–545. (From: Hospital for

Special Surgery, New York Hospital-Cornell University Medical College, New York, N. Y.)

Since the original roentgenographic visualization of the spinal cord in 1919, many different myelographic contrast media have been employed. Unfortunately, none has fulfilled all the requirements of an ideal contrast medium—no toxicity, complete and rapid absorption, good roentgenographic contrast, and miscibility with the cerebrospinal fluid. Therefore, the work set forth in this article is an attempt to compare, in laboratory animals, the roentgenographic and toxicologic properties of 3 recently developed myelographic agents.

The materials and methods are listed in detail, including the properties of the contrast media. Thirty cats were selected and divided into 5 groups. These were then laminectomized at the lumbar level and, under sterile operating room conditions, an equal volume, pre-determined "dose" of each of the following agents was placed into the subarachnoid space: (1) normal saline, for controls; (2) pantopaque; (3) SH 617L (myelographin); (4) ethiodol emulsion; and (5) conray (60 per cent). Posteroanterior and lateral roentgenograms were obtained immediately after injection and repeated just prior to sacrifice, at I week, 1 month, and 3 month intervals. The roentgenographic characteristics, toxicity, and absorption behavior were evaluated. Complete autopsies were done on all animals which died during the course of the experiment and, in all cats, the spinal cord and meninges were examined grossly and microscopically at cervical, thoracic, and lumbar levels.

These observations were tabulated and each contrast medium was graded on the basis of its subarachnoid pathologic effects and roentgenographic quality, realizing a limited correlation to similar effects and results in man. Normal saline, as expected, gave a completely negative result. The hypertonic, watersoluble conray appeared to cause the greatest overt reaction during injection but was consistently absorbed early and left no gross or histologic evidence of its presence. Pantopaque most often gave the best contrast for roentgenographic evaluation but always resulted in evidence of acute or chronic inflammatory reaction, usually transitory, and is the most poorly absorbed of the media tested. In all, 5 cats died, each death following injection by 2-11 days, 4 with myelographin and I with pantopaque. Each death was associated with a severe aseptic meningitis with I cat also showing myelomalacia and microabscesses and I cat showing anterior horn cell degeneration. Ethiodol emulsion was characterized by satisfactory contrast, no demonstrable toxicity and essentially complete absorption after myelography.

Further human studies are necessary to determine accurately the relative characteristics and clinical manifestations of these agents.—John Bond, M.D.

O'Malley, B. P. Some observations on nonoily myelographic media. *Clin. Radiol.*, Oct., 1965, 16, 405–411. (From: Roentgen Department, Ulleval Hospital, Oslo, Norway.)

The effects of cisternal injection of a water-soluble myelographic medium, sodium monoiodomethyl sulphonyl (abrodil, myelotrast or kontrast-U) on the central nervous system of rabbits are described in this paper. The autopsy findings in animals who died within minutes of receiving an intracisternal injection were essentially those of acute congestive heart failure (pulmonary edema and filling of the airways with pink hemorrhagic fluid). All animals receiving abrodil exhibited an immediate severe physical reaction, characterized by muscle spasms of the abdominal and limb muscles, opisthotonus, tachycardia and apnea succeeded by tachypnea. Neither intracisternal steroid nor antihistamine administration influenced these effects to any appreciable degree. Histologically, the appearances were within normal limits in 3 animals, and in 3 others there was only a slight menigeal inflammatory response, characterized by scattered foci of lymphocytes. Serial protein estimations and total white blood cell counts were done on the cerebrospinal fluid of the surviving animals and in all there was, at most, only a minimal variation as compared to the pre-injection values. The general physical condition of these rabbits appeared normal on the day following injection.

A recently developed contrast medium, B-(3-dimethylamino-methylinamino -2,4,6-triiodophenyl) propionic acid ethyl ester (SH 617L) was injected into 9 animals without modification, and in an additional 4 it was given along with a steroid and an antihistamine. There was no physical reaction, either immediate or delayed, following the injection of SH 617L, with or without modification. However, steep rises in the cerebrospinal fluid protein levels and total white blood cell counts occurred in all animals during the first 6 to 10 days following injection, gradually returning to normal values in the second week. This effect was not changed by the addition of the steroid (decadron) or the antihistaminic (polaramin). -Samuel G. Henderson, M.D.

Feigelson, Howard H., and Ravin, Herbert A. Transverse myelitis following selective bronchial arteriography. Radiology, Oct., 1965, 85, 663–665. (From: Divisions of Radiology and Medicine, Sinai Hospital, Detroit, and Departments of Radiology and Medicine, Wayne State University School of Medicine, Detroit, Mich.)

The authors report a case of transverse myelitis following bronchial arteriography performed via a femoral puncture using retrograde catheterization by the Seldinger technique. The right 4th and 6th inter-

costal arteries were opacified by test injections, without bronchial artery visualization. Injection into the right 5th intercostal artery demonstrated the right bronchial artery. A second injection of 5 cc. hypaque with serial filming then followed. The total injection dose throughout the examination was approximately 20 cc. A satisfactory study was obtained.

The patient subsequently stated that she noted involuntary contractions of the right knee during the procedure. This subsided but she was unable to void a few hours later. Flaccid paralysis of the right leg and paresis of the left leg ensued and there was sensory disturbance below the 5th intercostal level. These findings lessened over the next several weeks, but the patient still had some residual spastic right leg paresis 2 months after the arteriography.

The possible ethiologic factors are analyzed. Although the mechanism is not fully understood, the authors point out that the intercostal blood supply to the spinal cord is insignificant, and postulate an allergic or vasospastic reaction to the hypaque injection. They state that bronchial arteriography is not without hazard, and suggest that the examiner should be alert for any neurologic symptoms during the procedure which might indicate impending cord injury.—James A. Cunyus, M.D.

#### ABDOMEN

Janower, Murray L., Robbins, Laurence L., Tomchik, Frederick S., and Weylman, Walther T. Tannic acid and the barium enema. *Radiology*, Nov., 1965, 85, 887–894. (From: Department of Radiology, Massachusetts General Hospital, Boston, Mass.)

Two papers published in 1963 reported a total of 8 cases of hepatic necrosis and death presumed secondary to tannic acid in the preparation and/or the performance of barium enemas. Subsequent to this, in March 1964, the Food and Drug Administration banned the use of tannic acid in barium enemas as well as in preparatory enemas. Since this decision affects many radiologists, the authors have reviewed and evaluated the importance of tannic acid or similar compounds in the practice of radiology.

A retrospective study was instituted in which all cases of acute hepatic death at the Massachusetts General Hospital over a 17 year period from 1947 to 1963 were reviewed. Of the 76 patients who met the requirements for this study, 10 had received a barium enema from 1 day to 48 months prior to death. In only 1 of these cases was there the least suspicion that the barium enema was implicated. This case is reported in detail.

The authors conclude that there is insufficient evidence to link tannic acid with hepatic necrosis when tannic acid is employed for barium enema studies only (preparatory enemas excluded) and in known dosage. They feel that there is sufficient evidence to

indicate that tannic acid added to the barium suspension in the proper dosage is invaluable in improving barium enema studies. Any risk that might be entailed by its use may be less than from the disease that might otherwise be overlooked.—A. W. Sommer, M.D.

#### Skeletal System

RABINOWITZ, JACK G., WOLF, BERNARD S., GREENBERG, ELLIOT I., and RAUSEN, AARON R. Osseous changes in rubella embryopathy (congenital rubella syndrome). Radiology, Sept., 1965, 85, 494–499. (From: Departments of Radiology and Pediatrics, Mount Sinai Hospital, New York, and City Hospital, Elmhurst, N. Y.)

Cardiac anomalies, cataracts, chorioretinitis, deafness, and intrauterine growth retardation are abnormalities that may occur in the fetus as a result of maternal rubella infection during the first trimester of pregnancy. This paper describes the roentgen alterations in the bones observed in 7 newborn infants with intrauterine rubella infection.

The bone changes were predominantly localized to the metaphyses of the long bones, particularly the femoral metaphyses and consisted primarily of a disorganization of the bone structure with linear and ovoid areas of radiolucency alternating with coarse trabeculae. While the entire metaphyseal region occasionally appeared demineralized, the disorganized irregularity of the bone trabeculae was diagnostically more consistent. The normally smooth and sharp border of the metaphyseal-epiphyseal junction was interrupted by areas of rarefaction resulting in a frayed or dentate appearance. No metaphyseal cupping was observed in these cases. The proximal femora, humeri and the tibiae showed findings similar to those described above but to a lesser degree. Serial roentgenographic studies in the cases followed showed complete regression of all the visible bone abnormalities within 4 to 10 weeks. At no time was any periosteal reaction evident, and no clinical symptoms could be ascribed to the bone abnormalities.

The differential diagnosis should include congenital syphilis and congenital hypophosphatasia. Other bone changes and laboratory findings will help to differentiate. The consistent clearing of roentgenographic abnormalities rules out the presence of leukemia, neoplasm or a pyogenic osteomyelitis. Thrombocytopenic purpura is also a relatively common finding in the presence of intrauterine rubella infection and in all cases this disappeared within 2 months. Six of the infants studied showed an interfering agent in tissue culture compatible with rubella virus. The seventh infant was not checked for this as the mother had characteristic rubella during the first trimester and the infant showed bone changes and other congenital anomalies consistent with rubella embryop-

athy. Although the pathogenesis of the roentgen changes in these cases is not clear at present, it is felt that they may represent a viral form of osteomyelitis or a delay in endochondral bone formation associated with localized persistence of the rubella virus.

—Donald N. Dysart, M.D.

PILLAY, V. K. Ectrodactyly. Singapore M. J., June, 1965, 6, 110–115. (From: Department of Orthopaedic Surgery, University of Singapore, Singapore.)

Seven cases with so-called lobster claw-hand or claw-foot are reported. Six of the cases were in the same family and the genetic factors involved are discussed.

It is felt that this abnormality is closely associated with other hand abnormalities such as syndactyly and polydactyly, and that they all seem to be the results of an abnormal gene showing varying expression.—Alan G. Greene, M.D.

Witt, H. Die differentialdiagnostische Bedeutung der unvollständigen Hyperphalangie des Daumens für die Begutachtung. (The differential diagnostic significance of incomplete hyperphalangia of the thumb in disability evaluation.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, Oct., 1965, 103, 487-490. (Address: Chefarzt am Röntgen- und Strahleninstitut des Städt. Rudolf-Virchow-Krankenhauses, Augustenburger Platz, 1, 1 Berlin 65, Germany.)

This is a well illustrated report of 2 patients who had incomplete hyperphalangia of the thumbs in the form of bilateral, triangular, separate ossicles radially between the proximal and distal phalanges of the thumb. Ulnar deviation of the distal phalanx was evident clinically—and was known to be present in the mother and two children of one of the patients.

In each patient the question of a traumatic, rather than a developmental etiology was raised.—Henry G. Mochring, M.D.

MATLES, ARTHUR L. Identification of the inferior rim of the acetabular labrum on the arthrogram: an aid in the treatment of congenital dislocation of the hip. Bull. Hosp. Joint Dis., April, 1965, 26, 115-119. (From: Department of Orthopaedic Surgery, The New York Medical College, New York, N. Y.)

The author evaluated 190 arthrograms made on still-born infants. He compared these with arthrograms obtained in 14 living children, age 6 months to 5 years, who were being investigated for congenital dislocation of the hip.

He found that arthrography accurately localized the position, shape, and size of the femoral head, as well as the acetabular fossa. It also gave valuable information about the position of the fibrocartilaginous labrum, which on occasion is known to prevent adequate reduction of a dislocated hip; it appeared on the arthrogram as an indentation at the inferomedial margin of the acetabulum. This is an area that has previously been ascribed to the transverse acetabular ligament. The author refutes this assumption and points to the fact that this ligament is an internal structure closing the gap between the hyaline articular cartilage of the pubic and ischial contributions to the acetabulum. It, therefore, anatomically cannot cause a peripheral defect on the arthrogram.

The author describes in detail his procedure for performing arthrography in infants and older children

He concludes by stressing the importance of establishing the position of the labrum during arthrographic investigation of cases of congenital dislocation of the hip. This is extremely helpful in determining if an attempted closed reduction is truly concentric.—Kenneth M. Nowicki, M.D.

CLARK, PAUL M., and KEOKARN, THAMRON-GRAT. Popliteal aneurysm complicating benign osteocartilaginous exostosis: review of the literature and report of one case. J. Bone & Joint Surg., Oct., 1965, 47-A, 1386-1388. (Address: Dr. Clark, 721 Madison Avenue, Albany 8, N. Y.)

Seven cases of traumatic aneurysm of the popliteal artery caused by an adjoining osteocartilaginous exostosis were reviewed and an additional case is reported.

In most cases there was no cartilaginous cap but rather a sharp cancellous surface of protruding bone that injured the arterial wall. Associated trauma was frequent, and a painful mass was the chief symptom.

Such a complication of exostoses about the knee should be kept in mind by both radiologists and clinicians.—Arch H. Hall, M.D.

MALAWISTA, STEPHEN E., SEEGMILLER, JARVIS E., HATHAWAY, BETTY E., and SOKOLOFF, LEON. Sacroiliac gout. J.A.M.A., Nov. 29, 1965, 194, 954-956. (Address: Dr. Sokoloff, National Institutes of Health, Bethesda, Md.)

Both acute and tophaceous gout affect primarily the appendicular skeleton and characteristically spare the axial skeleton. In this paper the authors report on 3 gouty patients who were diagnosed as having associated sacroiliac gout. Two of the patients had clinically inactive, tophaceous involvement of the sacroiliac joints, manifested by multiple punched-out cystic areas of rarefaction with sclerotic rims which were present about the inferior two-thirds of these joints. The third patient had acute, recurrent, sacroiliac arthralgia, with discrete tenderness to palpation about the left sacroiliac joint, but roentgenographic examination of these joints revealed no abnormalities. This pain was unaffected by analgesics; however, the response to colchicine on a total of seven different occasions was always prompt. A presumptive diagnosis of acute sacroiliac gouty arthritis was therefore made. The total dosage of colchicine never exceeded 5 mg. in 24 hours.

The recumbent abdominal roentgenograms of 95 known gouty patients were subsequently reviewed retrospectively for possible sacroiliac changes. In 7 of these patients sclerotic-rimmed, punched-out cystic lesions of varying size in or near the articular surfaces were found, which were felt to be characteristic changes of gout. Osteophytes also projected from the inferior margins of these joints in 6 of the patients, and in each instance, advanced gouty changes were also present in the extremities. It was felt that fusion of the joints without cystic changes could not be attributed with certainty to gout rather than to spondylitis.

In an additional 5 patients variable pathologic changes were seen which were deemed to be consistent with, but not pathognomonic of, gout. These consisted of varying degrees of narrowing or obliteration of the sacroiliac joint space, mild to moderate irregularity of the joint surfaces, sclerosis of the joint margins, and marginal osteophytes. No cystic changes were present in this group.

It was concluded that acute sacroiliac gouty arthritis must be regarded as rare, but that chronic tophaceous gouty arthritis of the sacroiliac joints does occur with considerably greater frequency. It was suggested that a more minute examination of the sacroiliac joints with specialized techniques would probably detect more cases.—Donald M. Monson, M.D.

#### BLOOD AND LYMPH SYSTEM

EHLERS, CHR. Venographische Befunde bei der Schlüsselbein-Achselvenensperre (Paget-von Schroetter-Syndrom). (Venographic findings in occlusion of the axillary-subclavian veins—Paget-von Schroetter syndrome.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklear-medizin, Oct., 1965, 103, 464-472. (Address: Städtisches Krankenhaus Berlin-Wilmersdorf, Röntgenabteilung 1, Albrecht-Achilles-Strasse 59, Berlin 32, Germany.)

After discussing the etiology, pathogenesis, roent-

genographic anatomy and venographic technique of studying occlusion of the axillary-subclavian venous system, the author presents 2 case histories of posttraumatic venous thrombosis to illustrate his discussion.

The roentgenographic anatomy and findings are particularly well illustrated.—Henry G. Mochring, M.D.

Berlin, Leonard, Waldman, Irving, and Fong, John K. Occlusion of the inferior vena cava: a major roentgenographic abnormality with minor clinical manifestations. J.A.M.A., Nov. 29, 1965, 194, 984–986. (Address: Captain Waldman, USAF Hospital Wright-Patterson, Box 5035, Wright-Patterson Air Force Base, Ohio.)

It is paradoxical that occlusion of the inferior vena cava is accompanied by few and surprisingly mild clinical symptoms. Although it is usually not a fatal or severely incapacitating process, it is associated with a definite clinical syndrome consisting of edema of the legs, dilatation of abdominal veins, and, less often, varicosities of the lower extremities, varicocele, and hemorrhoids. When occlusion occurs superior to the level of the renal veins, albuminuria and ascites may develop. There might also be a disturbance in venous return from the liver.

The paucity of clinical findings in the majority of patients with this disease is best explained by the abundant collateral circulation available. Briefly, these pathways are: (1) superficial abdominal pathways; (2) gonadal veins to the renal veins; (3) intravertebral and extravertebral plexuses; (4) caval rudiments; (5) ascending lumbar pathway through the azygos and hemiazygos veins.

A definitive diagnosis of inferior vena cava obstruction can be made only by roentgenographic means—specifically, by inferior vena cavography. This may be accomplished by single femoral vein catheterization utilizing the Seldinger technique, with low pressure injection of contrast material using an automatic injector. In the 5 cases reported in this paper the obstruction of the distal vena cava was at the junction of the common iliac veins. When only collateral channels are identified, inferior vena cava obstruction can be presumed.

Another roentgen finding observed was scalloping of the ureter on intravenous urography. This has been previously described in such conditions as renal artery stenosis secondary to dilated periureteral collateral arteries, but has now laso been found with dilated, tortuous periureteral veins which were serving as collaterals to bypass the obstructed vena cava.

The commonest causes of vena cava obstruction are thrombosis and thrombophlebitis. When surgical

ligation or plication of the inferior vena cava for pulmonary embolization is being considered, vena cavograms prior to such operations could demonstrate a partial or complete occlusion, or significant collateral circulation. Under these circumstances ligation of some of the larger collateral vessels could be considered.—Donald M. Monson, M.D.

#### GENERAL

BEGHIN, J. Les aspects radiologiques de l'arthrogrypose. (Radiologic aspects of arthrogryposis.) J. belge de radiol., 1965, 48, 383–390. (From: Service de Radiologie, Hôpital Universitaire Brugmann, The Netherlands.)

Arthrogryposis multiplex congenita represents a cross-road of numerous congenital dysplasias. Basically it is an ankylosing myodysplasia which gives the fetus a rather fixed attitude and after birth it keeps the extremities habitually in flexion. The inertia of the fetus sometimes simulates fetal death.

Primary signs include the relative enlargement of the extremities which apparently is caused by increased subcutaneous tissue because the muscle tissue is actually decreased in size. There is shortening of the flexor muscles.

There are many secondary signs in associated malformations. These are listed as follows, the list not being exhaustive:

Head. Scaphocephaly, turricephaly, Cruzon's syndrome.

Brain. Microgyrie, absence of corpus callosum or rudimentary corpus callosum; hydrocephalus, cerebellar agenesis, hypoplasia of anterior ventricular horns, paralysis of sixth and seventh cranial nerves (Moebius' syndrome), absence of occular globe, and luxation of the crystallin lens (Marfan's syndrome).

Neck. Pterygiums or webbing of the neck, Klippel-Feil anomaly, scoliosis, kyphosis.

Spine. Diminution of interpedunciar spaces, agenesis of various portions (such as sacral agenesis), spina bifida.

Extremities. Dislocation of the hip, absence of one or more bones, fragile bones, arachnodactyly, polydactyly, microdactyly, and acrodactyly; absence of the patella and the sacrum are frequent; muscular calcifications may be present.

Heart and vessels. Involvement of muscular wall of vessels, aortic aneurysms, septal defects, telangiectasis and lymphagiectasias of hands or forearms.

Skin. Scleroderma, fragile skin, ungual hypoplasia.

Genital organs. Obesity with hypogonadism (Turner), Klinefelter's syndrome in male infants.—Charles M. Nice, Jr., M.D., Ph.D.

McCollum, Donald E., and Odom, Guy L. Alkaptonuria, ochronosis, and low-back pain: a case report. J. Bone & Joint Surg., Oct., 1965, 47-A, 1389-1392. (From: Division of Orthopaedics and Division of Neurosurgery, Department of Surgery, Duke University Medical Center, Durham, N. C.)

Ochronosis is an uncommon hereditary metabolic disease in which a deficiency of the enzyme homogentisic acid oxidase exists. The homogentisic acid produced by the utilization of phenylalanine and tyrosine is accordingly not metabolized further and is excreted in the urine or accumulated in tissues for which it has an affinity. Homogentisic acid when present in the urine causes it to turn dark brown or black on exposure to the air. The deposition of homogentisic acid in cartilage and other tissues with poor blood supply produces the clinical picture of ochronosis.

The earliest complaints are usually limitation of motion of the spine, hips, knees, and shoulders; there may be periods of acute inflammation resembling rheumatoid arthritis. Back symptoms occur early in the course of the disease, and the usual complaint is one of stiffness, rather than pain. No effective medical treatment or prophylaxis is known.

The physical findings are characterized by limitation of motion of the entire spine and loss of motion in the shoulders, elbows, wrists, hips and knees. The small joints of the hands and feet are spared. There is deposition of blue-black pigment in the ear cartilages and in the sclerae. Other findings may be the results of valvular heart disease, prostatitis, or renal stones.

Earliest roentgenographic changes occur in the thoracolumbar spine, where narrowing of the intervertebral spaces is followed by calcification of the annulus fibrosus and intervertebral disk as the disease progresses. Massive exostoses develop, and eventually interbody fusion occurs. By contrast, the osteophytes or spurs seen in hypertrophic arthritis are few, and calcification of the ligaments in this disease is minimum. Large joints in ochronosis show roentgenographic changes similar to those of advanced hypertrophic arthritis.

A case history is presented of a white male, age 34, with known ochronosis, in whom an acute low-back syndrome developed with findings of a ruptured intervertebral disk. Acute symptoms were relieved by removal of the ruptured disk and by a partial hemilaminectomy. On approaching the spine, a dark discoloration of the laminae of the fourth and fifth lumbar vertebrae was evident. The ligamentum flavum was also discolored. Within the spinal canal the posterior longitudinal ligament was discolored, and a bulging disk was found beneath the ligament at the fourth interspace. When the posterior longitudinal

ligament was incised, several black and gritty fragments of the disk extruded. The interspace was curetted and additional black calcified fragments were removed. Microscopic examination of these fragments revealed pigment deposition in fibrocartilage undergoing fibrinoid necrosis, with areas of calcification and mononuclear infiltration. The postoperative course was uneventful. Eighteen months after operation, the patient was completely free of pain.—

Stephen N. Tager, M.D.

Dworkin, Howard J., and Simeck, Charles M. Efficiency of molecular iodine removal from air. J. Clin. Endocrinol. & Metabol., Nov., 1965, 25, 1505–1510. (From: Department of Internal Medicine [Nuclear Medicine], University Hospital, Ann Arbor, Mich.)

The measurement of atomspheric iodine is of importance in an area where iodine balance studies are being done, as the presence of atmospheric iodine could produce an apparently negative iodine balance due to the uptake of the iodine by the respiratory epithelium. Several methods have been used to collect stable iodine from the air for subsequent measurement.

The authors describe two methods of trapping the iodine. They studied the efficiency of these methods. A generator was used containing a known amount of stable iodine as NaI<sup>127</sup> and a measured amount of radioactive iodine as NaI<sup>131</sup>. A potassium dichromate-sulfuric acid solution was used to release the iodine. The iodine was trapped either in a solution of sodium thiosulfate or by dry glass boiling beads coated with sodium thiosulfate. The trapping efficiency was then determined. The method using the glass boiling beads coated with sodium thiosulfate gave a trapping efficiency of greater than 90 per cent and was superior to the method using the sodium thiosulfate solution.

The advantages of the glass bead method are: it is inexpensive; dry; easily handled; well suited for field work; the extraction efficiency is high; the results are quite reproducible; and it gives a more accurate chemical determination of iodine.

No atmospheric iodine was detected by the above systems in the area where the iodine balance studies were being done (Ann Arbor, Michigan). There is a possibility that the chemical or physical form of stable atmospheric iodine may be such that the systems described here are of little value in extracting it.—Charles W. Cooley, M.D.

#### RADIATION THERAPY

Ariel, Irving M., and Lehman, Wallace B. Prognosis in patients with metastases to bone from primary breast cancer. *Bull. Hosp.* 

Joint Dis., April, 1965, 26, 40–46. (From: Soft Somatic Tissue Service, Hospital for Joint Diseases, and Pack Medical Foundation, Inc., New York, N. Y.)

One hundred and seventy-four patients known to have bone metastases from carcinoma of the breast were studied by the authors in order to determine the time interval between the onset of symptoms and the roentgen evidence of the metastases. Another 100 patients with proven breast carcinoma treated by radical mastectomy were followed for a period of 5 years or until their demise, whichever occurred first.

From this study the authors were able to draw the following conclusions:

Although none of the first group of patients revealed evidence of bone metastases at the time of the initial onset of pain, 90 per cent were found to have roentgen evidence of metastases within 6 months, and 49 per cent within 1 month.

Of the 100 patients in the second group, 29 died within 6 months of the onset of their bone metastases, another 36 between 6 months and 1 year, and another 24 between 1 and 2 years. Thus 65 per cent were dead within 1 year, and 89 per cent were dead within 2 years of the onset of bone metastases.

In general, the longer the period before the onset of metastases to bone, the better the over-all prognosis.

It was also found that most of the patients treated, whether by radiation therapy, surgery, radioactive isotope therapy, or chemotherapy, did obtain significant palliation.

It is, finally, concluded that patients complaining of bone pain following radical mastectomy, most likely have metastases to bone, and that approximately one-half of these will show roentgen evidence of metastases within 1 month. Thus vertebral pain in a patient following radical mastectomy for breast cancer, may be considered an indication for the initiation of anticancer therapy.—Kenneth M. Nowicki, M.D.

Baker, R. Robinson, and Weiner, Seymour. The clinical management of tonsillar carcinoma. Surg., Gynec. & Obst., Nov., 1965, 121, 1035–1038. (From: Department of Surgery and Division of Radiotherapy, The Johns Hopkins University School of Medicine, Baltimore, Md.)

Re-evaluation of present methods of therapy of malignant tumors of the palatine tonsil and tonsillar pillars was made to assess what advances could be attained. Sixty-six patients with biopsy proven malignant neoplasms were seen at Johns Hopkins Hospital and the Baltimore City Hospitals between 1948 and 1961. Ninety-two per cent were squamous cell

carcinomas and 8 per cent various types of lymphomas.

Operative treatment consisted of radical neck dissection and partial mandibulectomy and excision of the primary tumor.

Radiation therapy prior to 1960 was given utilizing orthovoltage roentgen rays. Since that time, patients received supervoltage therapy delivered by means of a 2 mev. generator.

After a review of the survival rates among these patients, the authors concluded that, although radical surgical excision was not associated with a prohibitive operative mortality, there is an appreciable morbidity. This was primarily due to resection of the musculature of the lateral pharyngeal wall. For this reason, irradiation of the primary tumor followed by a planned radical neck dissection seems to offer the best chance of cure or effective palliation.—Forrest Arnoldi, M.D.

HYMAN, GEORGE A. Management of metastatic cancer of the lung by newer chemotherapeutic agents. Am. J. M. Sc., Oct., 1965, 250, 374–380. (From: Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.)

The formerly hopeless attitude held toward metastatic cancer of the lung is considered no longer warranted by the author. Experience with over 1,000 cases has provided a guide for management of such a patient.

The over-all plan of treament must be carefully formulated. It is essential that the primary site be located by biopsy diagnosis. Areas of metastatic involvement are determined. Response to previous therapy is carefully evaluated. It is essential that the general condition of the patient be carefully evaluated, including estimation of hepatic, renal, marrow and pulmonary function. This evaluation is necessary for 2 purposes: (1) to eliminate the far advanced cases in which therapy would not only be useless but perhaps detrimental; and (2) to determine the preferred therapeutic agent, its dose and route of administration.

Radiation therapy is the treatment of choice for regional lesions which are radiosensitive. Occasional single pulmonary metastases, which are resistant to other forms of therapy, are managed best by local excision.

If irradiation or surgery is not indicated, chemotherapy is employed in symptomatic patients. Hormonal agents or ablative procedures may be used in endocrine or hormonally dependent tumors. Radiosensitive tumors are generally responsive to a variety of alkylating agents of the nitrogen mustard group. Radioresistant neoplasms may respond to 5-fluorouracil.—Forrest Arnoldi, M.D.

Rosvoll, Randi V., and Winship, Theodore. Thyroid carcinoma and pregnancy. Surg., Gynec. & Obst., Nov., 1965, 121, 1039–1042. (From: Departments of Pathology, Emory University School of Medicine, Atlanta, and The Washington Hospital Center, Washington, D. C.)

The authors in their study of thyroid carcinoma in childhood found 60 women who subsequently had I or more pregnancies.

In none of the 38 women who were clinically free of disease before conception did recurrence or metastasis develop.

In none of the 22 women who had concomitant thyroid carcinoma did they note any alteration in growth of the tumor.—Forrest Arnoldi, M.D.

ROBERTS, D. W. T., and HAINES, MAGNUS. Conserving ovarian tissue in treatment of ovarian neoplasms. *Brit. M. J.*, Oct. 16, 1965, 2, 917–919. (Address: Dr. Roberts, Consultant Obstetrician and Gynaecologist, St. George's Hospital, London, England.)

One hundred patients were treated at Chelsea Hospital for Women by unilateral ovarian cystectomy or cophorectomy during 1948-55. Of the 63 patients followed-up, 50 had benign neoplasms and 13 malignant.

When compared with 140 patients with bilateral ovarian carcinoma, of whom 28 per cent survived, only 1 patient with a benign cyst showed evidence of recurrent neoplasm, 1 borderline case developed recurrence and 9 out of 13 cases with definite carcinomas survived 5 years.

On the basis of these statistics the authors suggest that no further treatment be given to patients in whom carcinoma is an incidental finding in an ovarian cyst in a young woman.—Forrest Arnoldi, M.D.

#### **RADIOISOTOPES**

SMITHERS, D. W., HOWARD, NORMAN, and TROTT, N. G. Treatment of carcinoma of the thyroid with radioiodine. *Brit. M. J.*, Oct. 23, 1965, 2, 969–974. (Address: Dr. Smithers, Director, Radiotherapy Department, Royal Marsden Hospital; and Institute of Cancer Research, Royal Cancer Hospital, London, England.)

Thyroid carcinoma is not very common; a registration rate of only 1-2 cases per 100,000 population has been recorded. Probably no more than 15-20 per cent of the patients with cancer of the thyroid gland are likely to benefit from radioactive iodine treatment.

Preparation, equipment and procedure used for

therapeutic administration of  $\Gamma^{(3)}$  and rationale of the treatment and dosage are discussed.

The authors studied the effect of radioactive iodine treatment in 59 patients with carcinoma of the thyroid in the 14 year period 1949-62. These patients were selected from 196 cases with malignant tumors of the thyroid gland and were divided into two groups: (1) 29 patients who had local disease in the thyroid gland or the cervical lymph nodes, some of whom were postoperative with inoperable tumors or recurrent tumors; and (2) 30 patients who showed evidence of distant metastases, with no uptake, with limited uptake or with good uptake of radioactive iodine in the tumor.

Patients with anaplastic tumors in both groups showed no significant uptake of radioactive iodine and all did badly. Patients with differentiated tumors and good uptake of I<sup>131</sup> in both groups showed long regression and survival, including some with wide spread metastases.—*Abbas M. Rejali*, *M.D.* 

Sharma, S. M., Desai, K. B., Mehan, K. P., Ganatra, R. D., Mehta, M. N., Sundaram, K. and Antia, F. P. Diagnosis of hyperthyroidism by external liver counting: correlation between external scintillation counting of the liver and plasma protein-bound iodine. J. Nuclear Med., Aug., 1965, 6, 598-604. (From: Radiation Medicine Centre, Medical Division, Atomic Energy Establishment Trombay, Tata Memorial Hospital, Parel, Bombay-12, India.)

The authors correlated the external counting of the liver and the PBI<sup>131</sup> plasma determination following the oral ingestion of I<sup>131</sup> and related it to thyroid function. A total of 167 patients was studied: 70 euthyroid, 71 hyperthyroid and 26 with nontoxic goiters. The diagnoses were based on the clinical findings, thyroid uptake measurements and the determination of the plasma PBI<sup>131</sup>. The plasma I<sup>131</sup> and PBI<sup>131</sup> determinations were done 48 hours after the administration of approximately 25  $\mu$ c of I<sup>131</sup>. The I<sup>131</sup> thyroid uptakes were done at 2, 24 and 48 hours. The liver counts were done at 48 hours with the probe being flush with the body surface on the anterior axillary line over the percussed area of liver dullness

The normal I<sup>131</sup> uptake values at 2, 24 and 48 hours were  $13.3 \pm 6.5$  per cent;  $38.7 \pm 13.8$  per cent and  $41.1 \pm 13.2$  per cent, respectively. The normal PBI<sup>131</sup> value at 48 hours was  $0.099 \pm 0.063$  per cent of the administered dose per liter of plasma.

The external liver counting was found to clearly distinguish between euthyroid and hyperthyroid patients (t=10.2) and between hyperthyroid and nontoxic goiter patients (t=11.9). The correlation coefficient between the liver counts and the PBI<sup>33</sup> in

euthyroid and hyperthyroid patients was 0.84 and the correlation coefficient for hyperthyroid and non-toxic goiter patients was 0.76.

The advantages of the external liver counting over that of the plasma PBI<sup>151</sup> determinations are: the technique is simple; no additional well scintillation equipment is needed; no chemical contamination errors occur; and no venepuncture is necessary. The disadvantages are: liver and renal disease could produce false results; this test can not distinguish whether the I<sup>131</sup> is an inorganic iodide, protein-bound iodide or butanol extractable iodide; and it is not possible to separate the toxic from the nontoxic goiters when there is a borderline overlap of the liver counts.

The external liver counting test is a good check on the plasma PBI<sup>134</sup> determination.—Charles W. Cooley, M.D.

Burdine, John A., and Haynie, Thomas P. Diagnosis of pancreatic carcinoma by photoscanning. J.A.M.A., Nov. 29, 1965, 194, 979–983. (Address: Dr. Haynie, 6723 Bertner Avenue, Houston, Texas.)

No other cryptic malignancy offers a greater variety of nonspecific symptoms than carcinoma of the pancreas. Scintiscanning of the pancreas with selenomethionine Se<sup>75</sup> is the only direct measurement of its morphologic integrity short of exploratory laparotomy. At present the protocol that the authors use is to give an intravenous injection of 3  $\mu$ c selenomethionine Se<sup>75</sup> per kilogram (not exceeding 200  $\mu$ c) and to scan the pancreas 30 minutes later. Special diets, enzymes, and lead shielding have been dispensed with, but a liver scan with Au<sup>198</sup> is usually performed subsequently to exactly identify the size of the liver. Conventional scintiscanning equipment was employed.

A group of 29 patients suspected of having pancreatic disease was studied with scintiscanning and a normal appearance was noted in 14. In 10 of the 29 cases, the pancreas scan revealed "cold" defects ranging from small areas to nonvisualization of the organ. In 6 of these 10 cases surgical and pathologic confirmation of the diagnosis of carcinoma of the pancreas was obtained. In the other 4 cases with cold defects no definite diagnosis has as yet been established. Of the remaining 5 out of 29 patients, 1 with a clinical diagnosis of chronic pancreatitis had nonvisualization of the pancreas, and in the other 4 cases, enlargement of the left lobe of the liver obscured the pancreatic outline and made interpretation impossible.

This procedure resulted in visualization of the pancreas in most cases when no pathologic condition was present within the organ and the liver did not over-shadow the area of the pancreas. Pancreatic carcinoma and pancreatitis have usually resulted in diminution of radioactivity in the pancreas. Where the lesions are small (2–3 cm.) or peripherally placed, they may be missed as this is below the resolving power of presently available scintiscanners. The diagnosis of pancreatic carcinoma still is based on clinical grounds, and the diagnostic triad of pain, weight loss, and obstructive jaundice should be sought. Other ancillary symptoms and signs such as a palpable gallbladder, thrombophlebitis, and diabetes mellitus have to be evaluated.

Further clinical experience is necessary before it can be determined whether pancreatic scintiscanning will enchance early diagnosis and improve prognosis in pancreatic carcinoma.—Donald M. Monson, M.D.

Johnson, Philip M. Some diagnostic applications of combined radioisotope scanning of adjacent organs. J.A.M.A., Oct. 25, 1965, 194, 455-457. (Address: 630 W. 168th Street, New York, N. Y.)

Simultaneous radioisotopic scanning of 2 adjacent organs usually provides more information than separate scans of the organs. The correlation of the photoscans with the roentgenograms of the same area gives additional useful information. The author used 2 radioisotopes given at the appropriate time to study the chest and upper abdomen.

Patients received 10 drops of an iodine solution 3 times a day for 4 days prior to the scanning. A dose of 1.0  $\mu$ c/kg. body weight of Au<sup>198</sup> was given 30 minutes prior to the scanning for the combined lung-liver study; 5.5  $\mu$ c/kg. of I<sup>131</sup> sodium iodopamide was given 10 minutes before the scan for the combined lung-blood pool scanning. After the administration of 4.25  $\mu$ c/kg. of macroaggregated I<sup>131</sup> serum albumin, scanning was started immediately.

A scanning instrument with a 5 inch crystal and a 31-hole collimator with a 3 inch focus was used. The width and level of the window were adjusted to give similar count rates over the lung and liver when the Au<sup>198</sup> was employed. The window width was 100 kev. centered at 350 kev. In the other group, a window of 100 kev. width and centered at 364 kev. was used. Radioactivity levels of less than 10 per cent of peak values were excluded. The study required 40-60 minutes.

Two illustrative cases are presented. The first case had a pericardial effusion in which the chest roent-genogram was suggestive of a pericardial effusion and the scan showed a small cardiac blood pool. The other case had a mass in the left upper chest adjacent to the mediastinum, and the combined lung and blood pool scan showed no evidence of vascularity in the mass, thus excluding an aneurysm.

The combined radioisotopic scanning of the lung and liver or the lung and cardiovascular blood pool is of value in determining the presence of a pericardial effusion, the position of the diaphragm, questionably in the diagnosis of subphrenic abscess, and in differentiating thoracic aneurysm and neoplasm.—Charles W. Cooley, M.D.

MEEK, DAVID C., BROWN, DONALD W., SHMOCK, CARLTON L., and BLOUNT, S. GILBERT, JR. Demonstration of ventricular aneurysms by radioisotope scanning. *Radiology*, Nov., 1965, 85, 856–859. (From: Departments of Medicine and Radiology, University of Colorado Medical Center, Denver, Colo.)

Fourteen cases of ventricular aneurysm studied by scanning the heart following administration of  $3\infty \mu c$  of I<sup>181</sup> labeled iodipamide intravenously are discussed. A standard scanning device with a  $3\times 2$  inch crystal was used. Each scan was superimposed on an anteroposterior, supine chest roentgenogram. In this manner, satisfactory correlation between the cardiac silhouette on the roentgenogram and the scan was obtained.

In 4 patients, the aneurysm could be demonstrated on neither the chest roentgenogram nor the scan. In 5, the aneurysm was apparent on the roentgenogram, but the isotope did not enter the area, suggesting a thrombus within the aneurysm. In 5, the aneurysm was seen on the roentgenogram and was also seen on the scan, indicating that no thrombus was present.

The authors conclude that blood pool radioisotope scanning appears to be another method in the diagnosis of ventricular aneurysm, useful also in demonstrating in some patients the presence or absence of an intraluminal clot within the aneurysm.—Howard R. Stewart, M.D.

COHEN, ALBERTO, ZALESKI, EDWARD J., LUEBS, EIDE-DITTMAR, and BING, RICHARD J. The use of positron emitter in the determination of coronary blood flow in man. J. Nuclear Med., Sept., 1965, 6, 561-666. (From: Department of Medicine, Wayne State University School of Medicine, Detroit, and Harper Hospital, Detroit, Mich.)

Different isotopes, such as krypton 85, rubidium 86, K<sup>42</sup>, and radioiodinated serum albumin have been used for the measurement of coronary blood flow, and one single detector has been employed for recording precordial activity. With these methods the specific activity of heart muscle cannot be separated from that of the surrounding structures.

The authors used a positron emitter, Rb<sup>84</sup>, and a coincidence counting system to obtain a ratio between the myocardial uptake of Rb<sup>84</sup> and the arterial count which was proportional to the coronary blood

flow. The coronary blood flow is calculated by the logarithmic extrapolation of the myocardial clearance value of Rb<sup>84</sup> to zero time. All calculations were performed in a digital computor, and accuracy of the method was established in experiments on the isolated dog heart.

Coronary blood flow was obtained on 79 persons varying in age from 18 to 83 years. The coronary blood flows in individuals above and below the age of 40 and in females and males were not statistically different at rest. Also, the resting coronary blood

flows did not show significant differences in patients with and without coronary artery disease.

It was observed that sublingual administration of nitroglycerin in 12 individuals without coronary artery disease produced increased blood flow in 11 persons, but only 1 patient out of 10 with coronary artery disease showed raised coronary blood flow following sublingual administration of nitroglycerin and thus confirms similar reports by others using nitrous oxide methods or other isotope procedures.—

Abbas M. Rejali, M.D.



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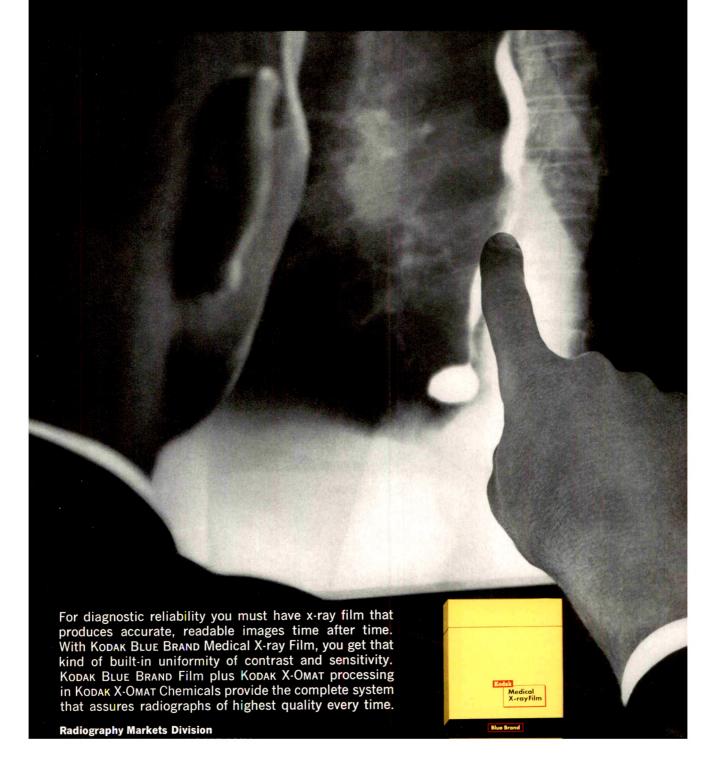
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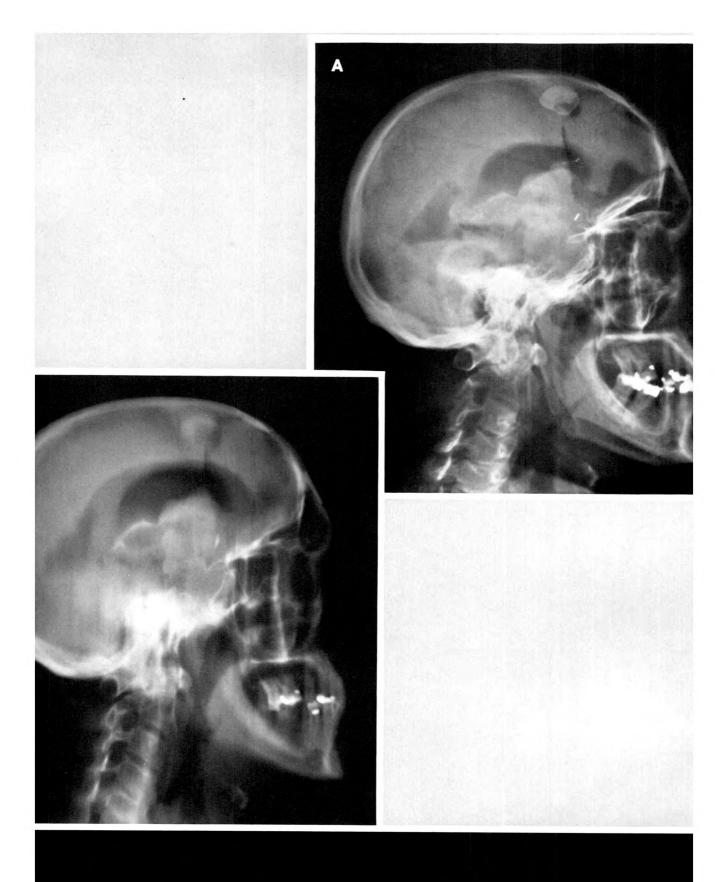
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# Diagnostic reliability





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## By ARTHUR M. MASTER, M.D.

Consultant Cardiologist, The Mt. Sinai Hospital, New York City; The U.S. Marine Hospital, Staten Island, New York; The Englewood Hospital, Englewood, New Jersey; and The Beth-El Hospital, Brooklyn, New York

### RICHARD P. LASSER, M.D.

Assistant Attending Physician for Cardiology, The Mt. Sinai Hospital, New York City

# ISADORE ROSENFELD, M.D.

Instructor in Medicine, Cornell Univ. Medical College, New York City

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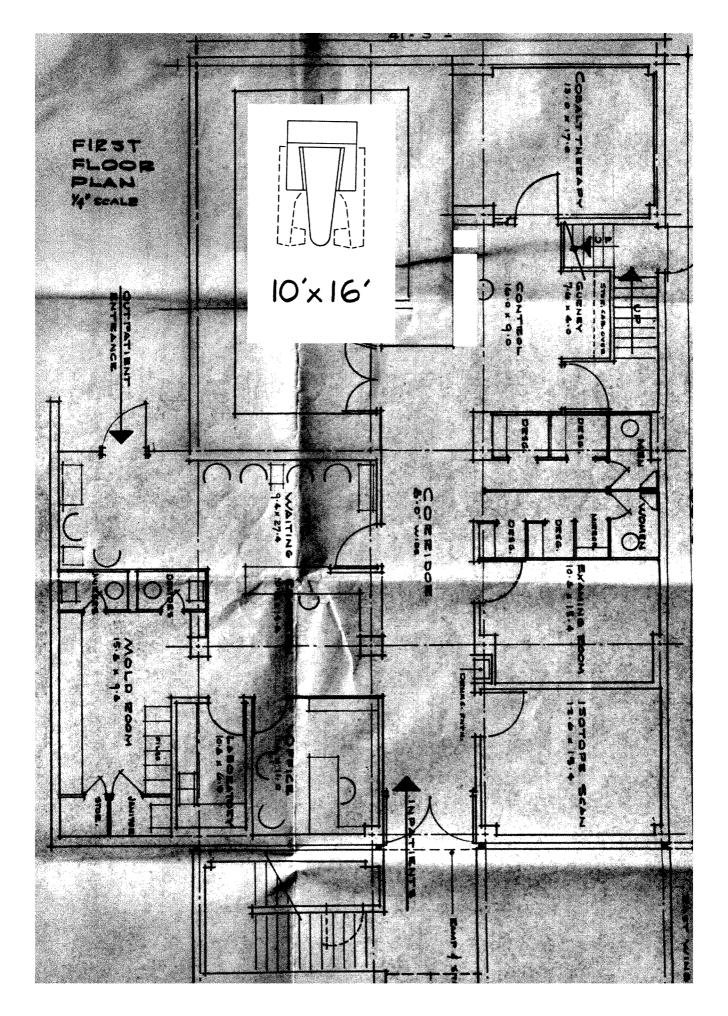
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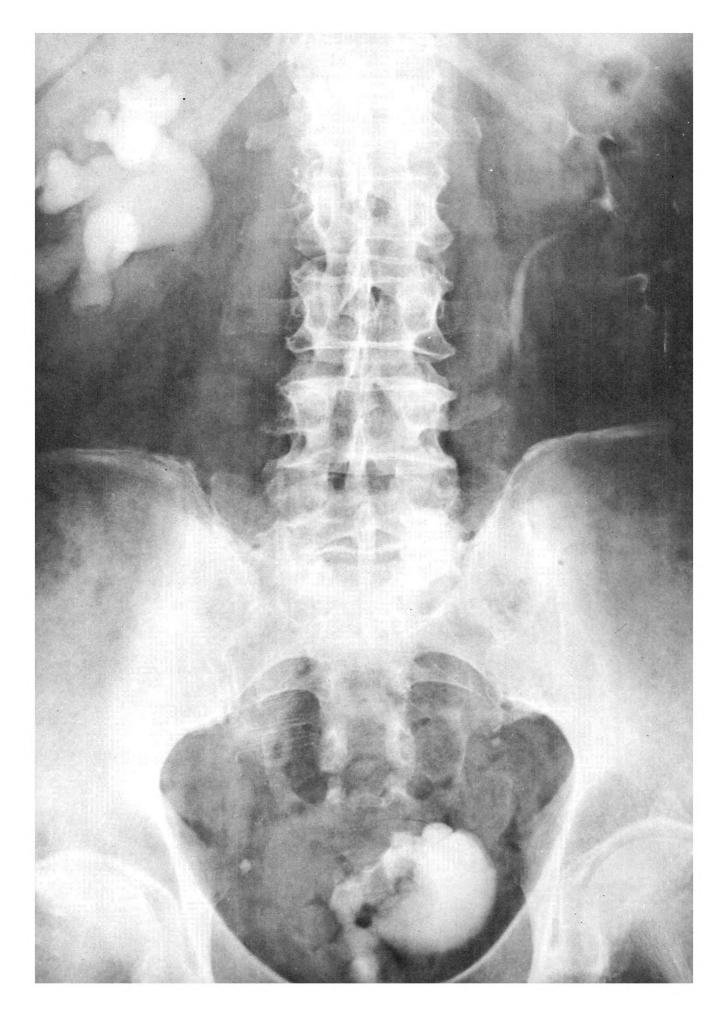
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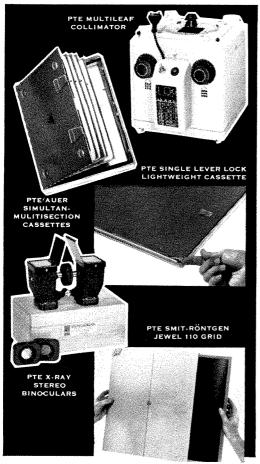
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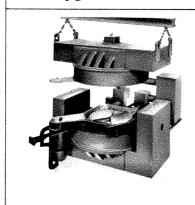
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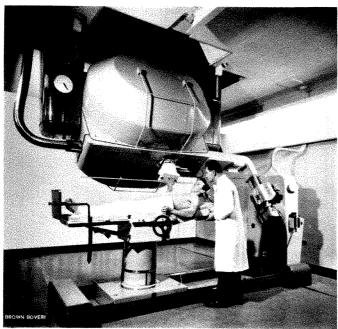
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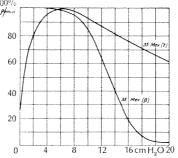
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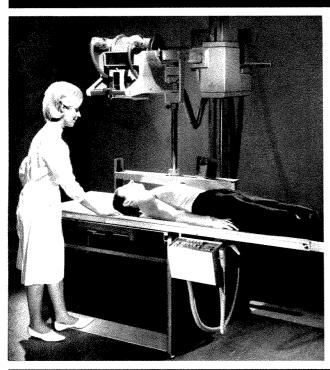
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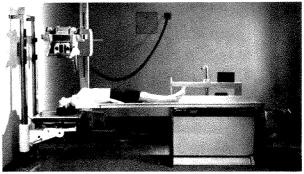
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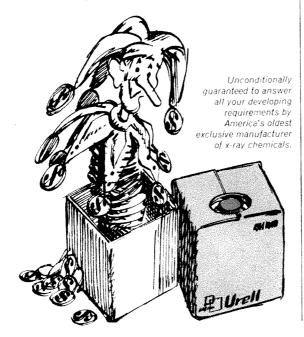
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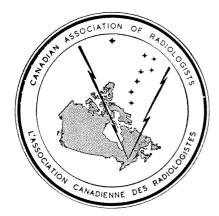
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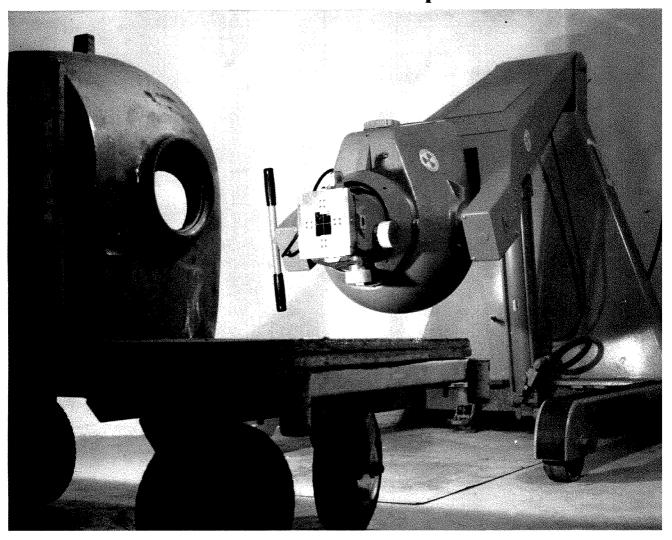
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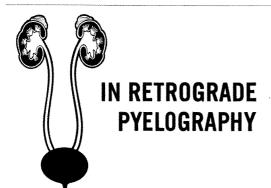
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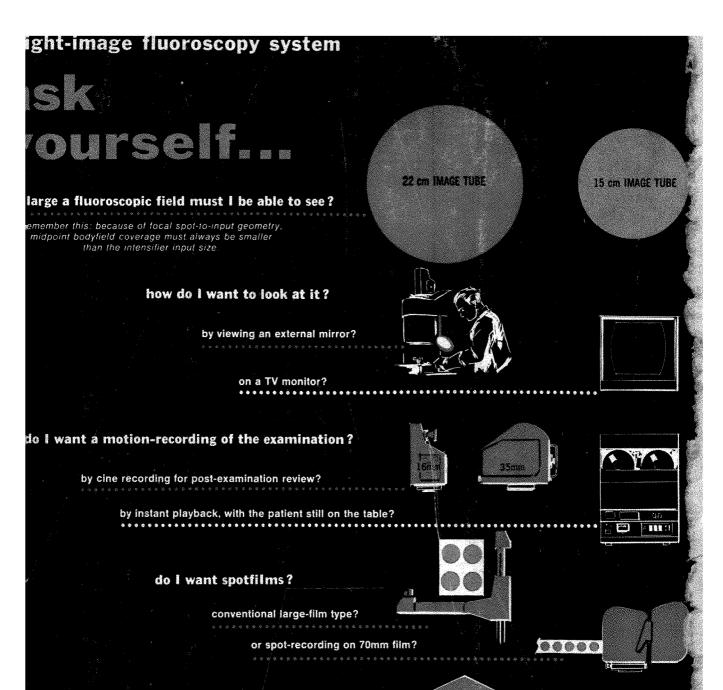
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